

NATIONAL INSTITUTES of HEALTH
NATIONAL INSTITUTE of CHILD HEALTH and HUMAN DEVELOPMENT

**Best Pharmaceuticals for Children Act
(BPCA)**

List Prioritization Review Panel

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Bethesda Marriott
Bethesda, Maryland

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[8:00 a.m.]

[Laughter.]

Review 4: Off-Patent Drugs

Dr. Stanley E. Grogg (for Dr. Susan Orenstein)

Now that I know Bob has his roots in Oklahoma,
the best of friends.

[PowerPoint presentation.]

1 DR. GROGG: Giardia, is an infestation, as we
2 are told, but it is the most commonly diagnosed
3 intestinal parasite in the United States. We see a lot
4 of kids that do end up hospitalized for failing to thrive
5 and abdominal bloating and some diarrhea. The national
6 average is about 10 per 100,000 population. It increased
7 in certain areas, such as New York City. Rates are
8 highest in young children, zero to five years of age.

9 Sources are domestic and wild animals. I know
10 I had a dog that had giardia, and the veterinarian told
11 me that it was contagious to humans. So this is one of
12 those things that people can get, actually, from animal
13 sources. Most commonly in day care, fecal-oral --
14 parents love that when you tell them -- and it can be
15 food-borne.

16 Low infection dose. It doesn't take a lot to
17 infect you, and symptoms include diarrhea, cramping,
18 weight loss, nausea, flatulence, and bloating, and can be
19 asymptomatic and mild and yet contagious.

20 The CDC MMWR Surveillance Summary of 2002,
21 Metronidazole Flagyl in most often prescribed in the
22 United States. It doesn't come in a liquid form, but the

1 tablet can be crushed up. Furazolidone was, although
2 less expensive, available in the United States by
3 suspension form, but it is no longer available in the
4 United States. There is another drug that is available.

5 Quinacrine is effective and inexpensive and is
6 available -- I haven't utilized that myself -- and some
7 of the other agents.

8 Albendazole, which is the drug that we are
9 talking about today, has been reported to be as effective
10 as the Flagyl with fewer side effects in two- to 12-year-
11 olds. Puromycin is not absorbed. Aminoglycoside is less
12 effective but used in pregnancy because it is less likely
13 to cause cancer. Flagyl can be combined with other
14 substances to help in the treatment.

15 Albendazole is poorly absorbed, and you need to
16 take it with a fatty meal. The benefits of Albendazole:
17 it is better tolerated than some of the alternatives.
18 It has a wide spectrum against potential coinfections
19 with other types of parasites.

20 In Africa, it is used every six months in
21 combination with other medications to deworm, if you
22 will, and that is probably where it came as a proposal to

1 be utilized for giardia.

2 Disadvantages. It requires at least several
3 days of dosing to obtain 90 percent effectiveness. There
4 are lots of studies that have been done, so it has been
5 looked at and evaluated.

6 In Task 1, Dr. Orenstein gave it a score of one
7 for information on PK. Unavailable, no studies, but you
8 do have quite a few studies that are out there. And zero
9 all the way through.

10 I will just go straight to the summary part.

11 The comments were, it has been studied in a
12 number of large pediatric RCTs internationally where
13 cases are more prevalent than in the U.S. Its efficacy
14 and safety appear relatively assured in children greater
15 than two years of age at doses of 400 milligrams for five
16 days.

17 You need to treat for a somewhat extended time
18 period for giardia, especially if dosing compliance is
19 assured by observation. That is part of the problem, is
20 the compliance, giving it five days in kids and 400
21 milligrams per day for five days. It should be given
22 with a fatty meal, so you send to McDonalds first.

1 Sustained efficacy is most likely if
2 infestation is prevented. Its benefits include low rate
3 and severity of side effects and concomitant therapy for
4 coinfection with other ailments or parasites.

5 The U.S. prevalence in children less than two
6 years of age is somewhat unclear. If there is a sizeable
7 population of such potential patients, further
8 information establishing dosage and safety in this group
9 would be worthwhile. Again, it is the most common
10 parasite infestation.

11 So she didn't make any particular
12 recommendations except to say only for limited study in
13 zero to two years, if there are enough children in this
14 age group who would potentially benefit by this drug's
15 availability.

16 So with that, on Table 2 she has some comments.
17 Dr. Orenstein says, indication to giardia. Pediatric
18 use, expand the use data on treatment of giardia and
19 other ailments. Adverse events, add column for giardia
20 treatment using the data from studies by Pengsaa and
21 Escobedo. Dosing for giardia in children and determine
22 and define dose in less than two years of age. Method of

1 administration to children unable to take tablets should
2 be specified. Can it be turned into a liquid form, in
3 other words.

4 You could use endpoints of giardia from the
5 stool. It is tough to find giardia in the stool
6 instantly. Those infectious disease people know that it
7 takes at least three stools a lot of times, and most of
8 the studies were done with two negative stools. They did
9 not use the INSOC test.

10 A rigorous RCT comparing Albendazole and Flagyl
11 and Furazolidone in children in the U.S. at doses now
12 believed optimal, including children less than two years
13 of age, would be useful to assess the efficacy and
14 comparable safety of these three medications.

15 So that is her recommendation.

16 **Secondary Review of Albendazole**

17 **Dr. Stanley E. Grogg**

18 [PowerPoint presentation.]

19 DR. GROGG: This is not a canned presentation.

20 I just want you to know that.

21 Albenza is the other name. It is approved in
22 the United States at the present time for hepatic

1 disease, which is echinococcosis -- I haven't had enough
2 coffee yet -- of liver, lung, and peritoneum caused by
3 the dog tapeworm in greater than two years of age and
4 neural cysticercosis -- I call my infectious disease
5 experts for these kind of diseases -- which is the pork
6 tapeworm, in greater than six years of age. So it has
7 some FDA approval in the United States at the present
8 time.

9 Giardia -- we always think of the board
10 question that I teach our residents -- is a teardrop-
11 shaped protozoan that you would see. You can see the
12 picture of it here. It lives in the small intestine and
13 is transmitted primarily when infective cysts are
14 ingested in water, fecal-oral contamination, and actually
15 from animals.

16 Clinically, it is passed via the fecal-oral
17 route. You have a little better diagram of the
18 organism. It causes severe abdominal cramps. I tell my
19 residents, it is a disease without fever, unless you have
20 coinfection, but they have a lot of gas passing, as in my
21 picture yesterday, and abdominal cramping. It is the
22 most frequent non-bacterial cause of diarrhea in North

1 America, so it is prevalent.

2 Albendazole is an anthelmintic type of agent.
3 It is a white powder. In Oklahoma, we are worried about
4 that statement for other reasons. It is practically
5 insoluble in water. At best, it is not very well
6 absorbed in the intestinal tract or from the intestinal
7 tract due to the low solubility. Negligible or
8 undetectable in the plasma, so you have to take it with a
9 fatty meal to get any systemic effect.

10 The systemic effect, though, is due to the
11 primary metabolite Albendazole sulfoxide. Again, you
12 need to go to McDonalds before you take it.

13 Maximum plasma concentration is two to five
14 hours after dosing, with an average of 1.31 micrograms
15 per mL following oral doses of 400 milligrams, and the
16 half-life is eight to 12 hours.

17 It is widely distributed throughout the body,
18 and it is excreted both in the urine and bile and broken
19 down in the liver. It can actually be found somewhat in
20 low quantities in the cerebral-spinal fluid.

21 It is converted in the liver primarily, as I
22 said, to metabolite, and urinary excretion is a minor

1 elimination pathway, with only 1 percent in the liver.
2 Most of it is in the biliary tract, where it is excreted.

3 So in pediatrics, it looks like there have been
4 some studies done that indicate at 10 milligrams per
5 kilogram, five patients six to 13 years of age, the
6 pharmacokinetics and the efficacy were similar to adults.

7 In less than six years of age, there were no problems
8 encountered safety-wise in a limited study.

9 Sixty-two children with giardia treated at 400
10 milligrams once daily for only three days only showed a
11 50 percent parasitology cure. That had a good P value in
12 this limited study with no major side effects.

13 So here are 150 children, two to 10 years of
14 age that received a single dose of 400 milligrams
15 suspension that they converted it into, with 22.5
16 milligrams per kilo per day, compared to the Flagyl three
17 times a day for five days.

18 For the five-day treatment, they got a 97
19 percent cure, so it looks like it does work if you give
20 extended treatment.

21 Three Albendazole and 20 of the Flagyl had side
22 effects, which included diarrhea, abdominal pain, nausea,

1 vomiting, weakness, and anorexia, but it did not
2 discontinue the use of the drug.

3 A pediatric giardia study in 165 Cuban children
4 treated with Chloroquine and Albendazole at 400
5 milligrams per day for five days, and Tinidazole, which
6 is not available in the United States. The Chloroquine
7 and Tinidazole cure rate was 91 percent and 86 percent
8 respectively, whereas the cure rate for Albendazole was
9 only 62 percent.

10 Microbiology. It has an inhibitory effect on
11 the tubulin polymerization, resulting in a loss of
12 cytoplasmic microtubials, for those that remember
13 microbiology from medical school. In the United States,
14 as I said, it has pork tapeworm and dog tapeworm as
15 indications for its use.

16 Contraindications. Rare fatalities have been
17 described, with granulocytopenia or pancytopenia, so CBC
18 monitoring at the beginning of each 28-day cycle is
19 indicated. Fortunately, this is quite rare in kids in
20 the studies that have been performed.

21 It is a category C. In pregnancy it may cause
22 fetal harm, and it has mild or moderate elevation of

1 liver transaminase when utilized, which is reversible
2 when discontinued.

3 Dexamethasone is a drug that causes changes in
4 drug levels. Adverse reactions include abnormal liver
5 function tests, abdominal pain, nausea, vomiting,
6 headache, dizziness, vertigo, reversible amnesia, versus
7 what some of us have, and fever.

8 So rare adverse reactions, as I mentioned, are
9 leucopenia, rashes, pruritus, allergic reactions, acute
10 renal failure. Again, rare in children, at least as it
11 has been studied so far.

12 Flagyl has been used in children and is
13 available in the United States. It is three times a day.

14 In the teenagers, you can't take it with alcohol, which
15 is a good thing. The potential cancer-causing effects,
16 though, are a concern for the pediatric population.

17 We do have a relatively new drug, Alinia. It
18 is a suspension approved by the FDA. I have used it a
19 couple times with very good success. It is approved for
20 giardia and cryptosporidium, so since Furoxone is not
21 available in the United States, this has kind of taken
22 the place as at least my drug of choice. I don't know

1 about infectious disease or giardia. So we do have
2 something else that is available.

3 Just looking at the cost, Albendazole is cheap
4 and can be crushed and turned into a liquid form. Flagyl
5 is somewhat more expensive, but Alinia is \$36 for a
6 bottle, which is pretty much a treatment course for kids.

7 In conclusion, we need to monitor liver
8 function studies and CBCs if using Albendazole. It is
9 not available in the suspension, but we can crush the
10 pill. It appears to need five days of therapy for
11 giardia, which can cause problems with compliance,
12 possibly.

13 So although Albendazole is somewhat efficacious
14 for giardia with only mild and transient side effects,
15 other drugs are available -- Alinia -- with better cure
16 rates and fewer side effects.

17 I was having a hard time scoring, Tami, these
18 particular score sheets, which I think they are good
19 because they bring to our attention what to look for. I
20 gave it a 10, but I recommend that this drug and
21 indication receive low priority for future listings and
22 discussion, whereas Susan gave it a three. It is just a

1 matter of, I read all those articles and I thought there
2 was a lot in the literature just because I looked at all
3 those articles.

4 With that, I would say if it was later in the
5 morning it would be time for a snack, but that is the end
6 of my presentation instead.

7 With that, whoever is next.

8 DR. WARD: Dr. Beckman, are you going to speak
9 for the FDA, or someone else?

10 **FDA Review of Albendazole**

11 **Dr. Joette Meyer**

12 DR. MEYER: I'm Joette Meyer. I'm a clinical
13 reviewer in the Division of Special Pathogen and
14 Immunologic Drug Products.

15 I would just like to mention that there are
16 actually two drugs approved in the United States for the
17 treatment of giardia in children. As was mentioned,
18 Nitazoxanide, or Alinia, was approved in November of
19 2002. It is available in a suspension form, and the
20 indication does go down to children one year of age.

21 The study in which Nitazoxanide was approved
22 was a clinical trial comparing three days of Nitazoxanide

1 to five days of Metronidazole, and Nitazoxanide was shown
2 to be non-inferior to Metronidazole.

3 Also, earlier this year, in May, the FDA
4 approved Tinidazole, or Tindamax, for the treatment of
5 giardia in children greater than three years of age.
6 Tinidazole is available as a tablet, but the tablets can
7 be crushed and dissolved in Karo syrup. There are
8 actually directions in the label for the extemporaneous
9 pharmacy compounding of the drug.

10 There are some articles in which Albendazole
11 has been compared to Tinidazole in the literature, and
12 actually, Tinidazole appears to be more efficacious than
13 Albendazole. There are also articles comparing
14 Albendazole to Metronidazole, and the two appear to be
15 more equivalent.

16 I think those are all of my comments.

17 **Open Discussion**

18 DR. WARD: Yes, Gary?

19 DR. OVERTURF: A couple of comments. First,
20 you don't need three stools to diagnose giardia any
21 longer and for at least a decade, because we have
22 molecular tests. Nobody recommends three stools for

1 giardia anymore. So it is actually a fairly easy disease
2 to diagnose because the tests have sensitivity way over
3 95 percent on a single stool.

4 DR. WARD: Are they PCR?

5 DR. OVERTURF: No, they are usually antigen
6 tests looking for one of the specific giardia antigens.
7 Most labs actually will not do full O & Ps which use a
8 microscope exam unless you indicate that you have a
9 patient from outside the United States in which you are
10 looking for anthelmintic pathogens.

11 One of the reasons why the Pediatric Infectious
12 Disease Society was interested in Albendazole is that
13 Albendazole is very useful. It is the only drug
14 available for a few things like echinococcus and
15 cysticercosis. Because that market is small in the
16 United States, we want to keep it licensed for giardia,
17 but we also would like to know how effective it is.

18 The other thing is that, practically speaking,
19 when you are treating patients with giardia, its failure
20 rates are very high with any single drug regimen. You
21 often have to use a second drug regimen. Albendazole, if
22 nothing else, provides one of those alternatives, and it

1 is a very well tolerated alternative.

2 The other thing is, we had made the comment
3 that we were a little bit surprised Metronidazole wasn't
4 on the list because it is a drug that really has not been
5 studied. It is another one of those situations that we
6 talked about yesterday which could still be used as a
7 comparator for many of these trials.

8 The biggest issue about Metronidazole that just
9 keeps coming up over and over again is based upon the
10 Ames pseudomonas test, which is this a carcinogenicity
11 issue. As far as I'm concerned, it is a non-issue. It
12 really has never been proven to be of any importance at
13 all in human biology as far as I'm concerned.

14 DR. WARD: I think it was also found in rats in
15 the bladder. That is my recollection.

16 DR. OVERTURF: Right. I think you are right.

17 So I understand these are problems, but they
18 remain on the label. They are problems that everybody
19 pretty much ignores, actually, clinically.

20 So I think Albendazole should be given a higher
21 priority. I don't know if it needs to be on the list
22 this year, but I think it needs to stay on there until we

1 have it appropriately niched. Maybe we need more data
2 before we make a final decision.

3 DR. WARD: Dr. Meyer, would you comment on
4 extemporaneous formulations of Albendazole? You
5 indicated Nutrasol, there are directions on the label for
6 that.

7 Have stability and solubility, and so on, been
8 looked at with Albendazole?

9 DR. MEYER: No, there is no information in the
10 Albendazole label, as far as making a suspension. I
11 think it's only -- I forget the tablet strength.

12 DR. WARD: It is 200.

13 DR. MEYER: Two hundred? And the dosing in
14 pediatrics is 15 milligrams per kilogram per day. So it
15 would have to be adjusted to the 200 tablet.

16 DR. WARD: I guess a related question would be
17 Nutrasol for cysticercosis. Has that been looked at?
18 Here we already have a suspension form, right?

19 DR. MEYER: Nitazoxanide is in a suspension
20 form.

21 DR. WARD: Has that been looked at for the
22 tapeworms?

1 DR. MEYER: No.

2 DR. WARD: Thank you, Dr. Grogg and Dr. Meyer.

3 Again, same scoring system as yesterday. Blue
4 sheet today. Put your names at the top and register your
5 votes for Albendazole.

6 DR. WIEDERMAN: Can I just ask, we are voting
7 on Giardiasis, not neural cysticercosis?

8 DR. WARD: Correct.

9 DR. WIEDERMAN: A Trojan horse from the
10 Pediatric ID Society.

11 [Laughter.]

12 DR. MATHIS: I'm going to go back to the
13 Pediatric Infectious Disease Society to ask two
14 questions. First of all, Metronidazole is off-patent, so
15 if you have recommendations that it appear on the list,
16 you may want to provide that input to NIH next year for
17 the 2006 list.

18 Then, on top of that, are you saying that you
19 were hoping that Albendazole would stay on the list to
20 make it remain available for other indications other than
21 giardia? So, you want to see it remain on the market for
22 other indications, not for giardia?

1 DR. OVERTURF: Actually, I think both. Some of
2 the data that we reviewed by Dr. Grogg I think is
3 interesting in that it has had a checkered past. I guess
4 I would have to examine those studies a little more
5 carefully, because there are two issues here.

6 This is very much like dealing with
7 Streptococcal pharyngitis. Some studies look at
8 microbiological success, and so eradication of the
9 organism. Other studies look at elimination of symptoms.

10 I suspect that most of those studies that showed low
11 rates were primarily looking at eradication of the
12 organism. That may not correlate with symptoms.

13 The background rate of giardia in developed
14 countries is in some places just a little less than 5
15 percent. In other words, 5 percent of us around this
16 room are sitting here with giardia and living with it
17 quite well, thank you very much.

18 [Laughter.]

19 DR. OVERTURF: So the issue would be, who is
20 having symptoms.

21 The tapeworm infection is probably much less,
22 but most of you will not be symptomatic with tapeworms

1 until I tell you you have one.

2 [Laughter.]

3 DR. OVERTURF: So I would like to leave it on
4 the list for both continued examination and studies. I
5 hate to say eliminate it for other indications.

6 That was actually a confusing issue of the
7 whole process here. We had to address drugs in a very
8 specific way, and then when we got requests to review and
9 come here on the panel, we got very focused reviews at
10 times that I thought sometimes we didn't think were even
11 pertinent, like the issue of Cefuroxime and sickle cell
12 disease and Cephalexin and oral infections and so forth.

13 Yet there are broader issues for those drugs, and I
14 think that is true for Albendazole.

15 DR. LASKY: I just want to clarify a couple of
16 things, because it is becoming clear to me the problems
17 that we are having in the process.

18 When we sent the outreach, we were required to
19 have the outreach to the public go in a very open manner
20 so that it does not appear to be a survey. If it is a
21 survey, it has to go through clearance to the Office of
22 Management and Budget, and it could be held up by over a

1 year, apparently.

2 So we were told in wording the outreach that we
3 had to make the outreach as open and voluntary.
4 Basically, if you care to take this opportunity and share
5 your thoughts with us, please do. I have been thinking
6 about this since last night as well. The outreach really
7 needs to be more structured, but then it comes into
8 conflict with this OMB regulation that we are not allowed
9 to go and survey the American public, basically is what
10 that thinking is.

11 So we may be stuck with an open-ended outreach
12 that then gets funneled into this much more specific
13 process, which is, I think, one of the problems that we
14 are dealing with.

15 The other point, Metronidazole was mentioned by
16 the Pediatric Infectious Disease Society in this letter,
17 and I think we discussed it. I'm sure in our notes we
18 can find out why we didn't put that on the list but did
19 put Albendazole on the list.

20 What we tried to do is when we did receive the
21 outreach is, we did review it not only in the working
22 group but FDA went back to the review divisions. There

1 were conversations that took place, but it is clear then
2 that this is an area of interest and needs further
3 thought, if nothing else.

4 DR. WARD: I have a couple of things. One is
5 that at the end of the day we want feedback about
6 process. One of the things that has arisen since the
7 beginning of this BPCA process is that those in the
8 clinical arena and carrying various hats of expertise in
9 specific therapeutic areas may have in mind specific
10 drugs that need to be studied in a specific area or in
11 general areas. Then, when it gets translated to requests
12 for studies by the FDA divisions, that focus may miss the
13 mark that we had in mind.

14 I think to the degree that we can figure out
15 how to reconcile that disconnect we can improve things,
16 again, to serve the needs of children better, so that we
17 can encompass what we see in the clinical arena but the
18 division reviewers may not be as aware of.

19 Yes.

20 DR. MATHIS: I have to admit I was talking to
21 Don about how we could feed this information back to the
22 review divisions and then next year possibly have them

1 come back for indications that we have heard around the
2 table over today and yesterday.

3 So, yes, this information can be used. I'm
4 sorry.

5 DR. WARD: I didn't mean to put you on the
6 spot.

7 DR. MATHIS: That's okay.

8 DR. WARD: Stan.

9 DR. GROGG: Just a final comment. One of the
10 endpoints of the studies that I reviewed, they all did
11 stool evaluation, and since the cyst is found in the
12 duodenum, it may not be present in the stool. So whether
13 they were really cured or not is a question. Now that we
14 have better techniques for diagnosing giardia, I would
15 suggest that any studies that might be done use the newer
16 techniques.

17 DR. WARD: Let's move off of the infestation
18 area.

19 Dr. Zaoutis, do you want to discuss
20 Clarithromycin for oral infections in dental patients?

21 **Review of Clarithromycin**

22 **Dr. Theoklis E. Zaoutis**

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1 DR. ZAOUTIS: Our task was to evaluate
2 Clarithromycin for oral infections. Clarithromycin is a
3 macrolide class antibiotic that is available in several
4 formulations: extended tablets, regular tablets, and the
5 granules for oral suspension.

6 There is very good PK and PD data in children,
7 including dosing guidelines based on weight that appear
8 in the label.

9 The Metaworks group has put together a nice
10 review of the studies, and they identified 82 pediatric
11 studies in which Clarithromycin has been evaluated.
12 Included in those are 14 randomized clinical trials, two
13 non-randomized trials, and 14 cohort studies.

14 The current indications for use in which
15 efficacy has been established include pharyngitis,
16 tonsillitis, community-acquired pneumonia, sinusitis,
17 otitis media, uncomplicated skin and soft tissue
18 infections caused by Staph aureus and Group A strep, and
19 disseminated mycobacterium avian infection.

20 PARTICIPANT: And H. pylori.

21 [Laughter.]

22 DR. WARD: Here comes a small voice from the

1 right. Any other voices?

2 [Laughter.]

3 DR. ZAOUTIS: It is a relatively well tolerated
4 drug with the most common side effects being
5 gastrointestinal: vomiting, diarrhea, and abdominal pain.

6 There are rare severe events, including cerzapoints and
7 ventricular tachycardia associated with prolonged QT
8 interval with the macrolides, as well as with this
9 macrolide, specifically.

10 It is an inhibitor of the P450-3A isomer, so it
11 has potential for interactions with other drugs.

12 Specific to oral infections, as we discussed
13 yesterday with Keflex or Cephalexin, oral infections tend
14 to be polymicrobial and include anaerobes. The label
15 lists several anaerobic bacteria that Clarithromycin has
16 activity against. The label suggests that the data is in
17 vitro only, and the drug has not been evaluated
18 clinically for the treatment of infections caused by
19 anaerobes.

20 In addition to the Metaworks review, there is
21 some literature in the treatment of oral infections, and
22 the studies break down into two categories, one looking

1 at in vitro data against anaerobic bacteria and the other
2 sort of case reports and less rigorously done studies.

3 The in vitro data, including one study looking
4 at Clarithromycin's activity against anaerobic bacteria
5 identified in pediatric patients suggested that it has
6 some activity against some of the anaerobes. There are
7 several other papers using adult isolates of anaerobic
8 bacteria that suggest that it has, again, reasonable
9 activity against some of the anaerobes.

10 Clinically, there is a double blind randomized
11 control trial that appeared in the Japanese Journal of
12 Antibiotics which revealed a response rate of 77 to 88
13 percent for Clarithromycin when used for oral or dental
14 infections. There is also a dental study that was non-
15 randomized of 41 patients that suggested it worked well,
16 although the details were not available.

17 The Journal of the American Dental Association
18 has also published a systematic review which mostly
19 consisted of case reports anecdotally reporting success
20 in the treatment of oral infections with Clarithromycin.

21 Finally, the Cochran Group looked at one study
22 for the prevention of mucositis in cancer patients, and

1 used Clarithromycin to prevent mucositis and found
2 borderline significance.

3 So in filling out this task scoring worksheet,
4 I had a little bit of difficulty, as mentioned by the
5 other reviewers. There is a lot of PK and PD data for
6 this drug, although not for this indication. There is a
7 lot of safety data and a lot of efficacy data for this
8 drug, again not specifically for this indication.

9 I'm assuming that the request from the Dental
10 Association had to do with the treatment of panallergic
11 patients, but that is an assumption.

12 In looking at the rest of the questions on this
13 list in terms of the severity of the disease and whether
14 this is a leading diagnosis that leads to
15 hospitalization, prolonged hospitalization, chronic
16 disability, I do not feel that was important. It does
17 have a very good therapeutic index, and there are other
18 alternative therapies that are effective and safe.

19 So I scored it as a priority three and did not
20 recommend that it appear on the list anymore.

21 DR. WARD: Dr. Woods?

22 **Secondary Review of Clarithromycin**

Dr. Charles R. Woods

DR. WOODS: I think I don't have a lot to add to that. I wasn't sure what the indication was that we were looking at.

For oral infections, I guess I would just echo, I don't see that this has much of a role unless there is some interesting in panallergic patients. I think there may be a role to study it for other indications: cystic fibrosis where actually in biofilms it may actually have some potency against pseudomonas. There may also be some immunomodulatory impacts, some thinking along that line, although I sort of suspect it actually is an antibiotic more than an immunomodulator in that condition.

So that would be the place I would say it might be deserving of further study, but I also gave it a priority three, the same score.

I would, maybe, recommend it for study for another indication but not for this indication. So for this indication, I would not recommend it.

DR. ZAOUTIS: The voice from beyond became the hand from beyond and handed me the book from the request for this. Actually, in their request, they say that

1 "The recent literature for adult dental patients suggests
2 that the susceptibility of oral pathogenic
3 organisms to Clarithromycin is low and the
4 propensity of macrolide impacts to inhibit the
5 CYP3A4 across a multitude of pharmacokinetic
6 adverse drug reactions mitigate against routine
7 use of this class of antibiotics."
8 Then they go on to say that it should be
9 studied.

10 DR. WARD: With EKG monitoring.

11 [Laughter.]

12 DR. WARD: Who is speaking for the FDA? John,
13 okay.

14 **FDA Review of Clarithromycin**

15 **Dr. John Alexander**

16 DR. ALEXANDER: I don't think I have much to
17 add to this, either. I mean, Clarithromycin is a drug
18 that is available as a syrup. It is labeled. It has a
19 funny metallic taste to it. It has the same issues with
20 Erythromycin with regard to potential for QT prolongation
21 and SIP 3A4 interactions. The only sort of advantage to
22 it over the Erythromycin is that it has a longer half-

1 life and it allows for BID dosing of the drug.

2 The activity against anaerobes is variable.

3 The information on the anaerobes that is in the label to
4 which the reviewer referred was basically information
5 that we have on in vitro data that was submitted for some
6 of those organisms. When I was trying to look into some
7 of the information on other anaerobes, the data there are
8 variable. So there are some reports where for
9 peptostreptococci and some of the oral floor that MIC50s
10 and MIC90s are a little bit higher.

11 So I do think that there are other drugs that
12 are available as alternatives for treatment of oral
13 infections.

14 **Open Discussion**

15 DR. WARD: Gary.

16 DR. OVERTURF: Again, the request is misplaced
17 because there are needs for Clarithromycin data,
18 particularly for, for instance, pertussis prophylaxis in
19 neonates, where there are virtually no data. There are
20 no data, and there is really no PK and PD in that group.

21 One of the things that was not mentioned is its
22 safety. Nobody takes 14 days of Erythromycin, nobody,

1 zero. You might get it down a kid because you can just
2 stuff it down them.

3 The major advantage of the new macrolides is
4 that they do not cause the GI distress that is caused by
5 Erythromycin, and they have no potential to do so. So
6 for those indications which are prolonged treatment
7 regimens, they both shorten the course of those treatment
8 regime, or potentially, and they may avoid some very
9 serious adverse events, like some of the problems we have
10 had in neonates with Erythromycin.

11 So again, this is a drug that needs to stay on
12 the list but for a different reason. This oral infection
13 has nothing to do with anything. I agree it should be
14 off the list for oral infections.

15 DR. WOODS: The other comment to make is that,
16 in pediatrics, in terms of macrolides, Azithromycin has
17 sort of supplanted Clarithromycin in many ways, partly
18 because of taste and the shortened course, but there are
19 rising concerns that, I guess, the kinetics of the white
20 cell and its persistence inside white cells at sub-MIC
21 levels may drive resistance to macrolides.

22 So I do think we need to have different types

1 of information for this, not for oral infections.

2 DR. WARD: Another word from the FDA.

3 DR. SNODGRASS: If I might add another comment,
4 I don't know how many years you can keep a drug on a
5 list. Clarithromycin was dismissed last year.

6 DR. MATHIS: We can come back every single year
7 and discuss this drug.

8 DR. SNODGRASS: Until 2007.

9 [Laughter.]

10 DR. SNODGRASS: It was dismissed last year as a
11 "me too" drug, if you will remember, but for another
12 indication. There have been some post-marketing reports
13 on Clarithromycin, and those include some allergic
14 reactions as well as some dental discoloration. So
15 certainly, those people who are prescribing it will see
16 some of these adverse events, but it is reversible.

17 Otherwise, I agree with the other remarks made
18 by the reviewers and Dr. Alexander.

19 Thank you.

20 DR. WARD: Gary, could you comment about
21 Azithromycin for pertussis in neonates?

22 DR. OVERTURF: Actually, there is more data on

1 Azithromycin in general for things like pertussis
2 prophylaxis. Most of it is European data, some of it is
3 Canadian data. I think the Canadian study, though, was
4 with Clarithromycin, if I'm remembering right.

5 So again, this may be nothing more than an
6 issue of labeling, except for some of the PK and PD data
7 that affects neonates, which this is a frequent
8 indication because that is the group who needs pertussis
9 prophylaxis the most.

10 So I just reviewed the pyloric stenosis and I'm
11 totally convinced that Erythromycin is associated with
12 pyloric stenosis.

13 DR. WARD: Actually, that is not a new issue.
14 If we hadn't been in this process, we probably would have
15 known that in the 1950s, because the data on that is that
16 old.

17 DR. OVERTURF: The first report I found was in
18 '76, and it was actually very poorly done.

19 DR. ALEXANDER: Actually, that is a point here,
20 because, I mean, in terms of Clarithromycin, what
21 Clarithromycin is is 6-O-methyl-Erythromycin. It is the
22 same drug with a methyl group on the end of it.

1 There are studies that we have requested for
2 Azithromycin, based on this off-patent written request
3 process for two different indications. So it's not
4 pertussis prophylaxis but it's ureaplasma infection, and
5 for chlamydia. They are both including PK information on
6 Azithromycin down to pre-term neonates because of the
7 ureaplasma question. So we will have more information
8 that will be available on the PK of that drug.

9 I think that in terms of trying to select drugs
10 for priority, I would still look at the potential for
11 Azithromycin as the drug to use for treatment of
12 pertussis over Clarithromycin just because of the
13 concerns of its relatedness to Erythromycin and the
14 pyloric stenosis issue.

15 DR. MATHIS: Just real quickly, I would like to
16 say that even though one year we might decide that a drug
17 should not be placed on the priority list for the
18 indication that we looked at it for that year, that we
19 need to keep the discussions open. We learn new things
20 and we develop new resistances or new use patterns.

21 So even though we may dismiss a drug from the
22 priority list this year or last year, there is no reason

1 why we may not discuss it again next year. So keep
2 giving us your ideas about how you would like to see
3 these drugs used, and we will keep discussing those
4 issues. We need to keep reevaluating all of these drugs
5 as we go through this process.

6 DR. WARD: One of the things we did yesterday
7 was to have write-in aspects about indications. I think
8 having those recorded is helpful to the agency, and it
9 preserves our thoughts and our discussion in a very clear
10 fashion. I would suggest, as Dr. Overturf pointed out,
11 two of these, the tapeworms for Albendazole and other
12 indications for Clarithromycin, to feel free to write
13 those in if you feel that those need to go back to the
14 agency as potential areas that need to be studied in the
15 future.

16 DR. MATHIS: To write them in after scoring the
17 current indication.

18 [Laughter.]

19 DR. WARD: Yes, Stan.

20 DR. GROGG: I hesitate to say this because my
21 son works for a pharmaceutical and part of his salary
22 comes from --

1 PARTICIPANT: Full disclosure.

2 DR. GROGG: Full disclosure.

3 In addition to the metallic taste, it is kind
4 of back to the septum issue. You get that first dose
5 down, but that second dose, unless you like to eat sand,
6 it is almost impossible because it gives that sand-like
7 consistency in the mouth for at least three hours, I can
8 tell you personally, having tried it, thank you.

9 DR. WARD: Wayne.

10 DR. SNODGRASS: So there are studies on taste,
11 particularly young children's preference for taste.
12 There was a study in one of the pharmacy journals several
13 years ago, and black cherry came out first, as an
14 example. My point is this, that for oral antibiotics and
15 other oral drugs, this is a real issue in pediatrics. If
16 you are in the position of prescribing for children, they
17 will come back to you that day maybe upchucking, and you
18 have to deal with it. These are big problems.

19 DR. WARD: The whole issue of compliance. It
20 is not like you are going to reason with them.

21 DR. SNODGRASS: No, no, you are not.

22 [Laughter.]

1 DR. SNODGRASS: Is there any kind of discussion
2 with drug companies or through the agency about dealing
3 with this in some more general manner?

4 DR. MATHIS: We actually do at times ask for
5 palatability, and then we also do the intent to treat
6 studies. So if a kid can't complete a course of therapy
7 because they are throwing it up, that becomes a review
8 issue for us.

9 But you are right. We have actually done some
10 internal studies on palatability for things like --

11 PARTICIPANT: Doxycycline.

12 DR. MATHIS: Doxy we did; for iodine we did.
13 So there are different compounding reasons why we have
14 looked at palatability, and it is a big issue.

15 DR. WARD: In about I want to say '98 or '99,
16 there was a meeting about formulations for pediatrics
17 specifically about that, and that may warrant redoing the
18 whole issue of taste as a special science.

19 DR. MATHIS: It really is in the best interest
20 of industry to make their formulations palatable because
21 otherwise people start talking about their drug like we
22 have been talking about the drugs around this table. We

1 are all practicing pediatricians, and we know what not to
2 give our patients so they don't come back throwing up.

3 DR. ALEXANDER: I do think that you need to
4 recognize that this is a difficult issue for the industry
5 as well. I mean, I have dealt with them on a lot of
6 issues with regard to the tastes and formulations of
7 different products, and sometimes it doesn't matter what
8 flavors that you add to something, a drug just tastes so
9 bitter that you are not going to mask that poor taste.

10 So there is only so much that you can do that
11 is going to provide both the drug being able to get into
12 the system as well as covering the fact that you have the
13 taste issues and palatability of the drug.

14 DR. MATHIS: Dr. Alexander, I'm sure, can share
15 the experience that industry has had with HIV
16 medications. Everybody knows about Prelone, which is
17 cherry-flavored gasoline. The HIV medications have been
18 a real challenge for the division.

19 DR. WARD: There is an organization, U.S.
20 Pharmacopeia Convention, that has some superb formulation
21 chemists. This sounds like an opportunity for a role.

22 Stan.

1 DR. GROGG: Just a suggestion to the
2 pharmaceutical companies that we might refer back. If
3 they make it taste like gasoline or furniture polish,
4 kids seem to like those.

5 [Laughter.]

6 DR. WARD: Let's return to the infestation
7 world and talk about Ivermectin for scabies.

8 **Review of Ivermectin**

9 **Dr. Lisa L. Mathis**

10 DR. MATHIS: Ivermectin was new to me. We
11 don't have much of a problem with river blindness in
12 Portland, and so I was looking it up and thought, oh,
13 this is an interesting drug.

14 If you are not familiar with it, which I
15 wasn't, it is in the class of the Ivermectin broad-
16 spectrum parasitic agents, and it binds selectively with
17 high affinity to the glutamine gated crotamiton channels
18 in invertebrates. It does not cross the blood-brain
19 barrier.

20 It has been used extensively overseas. It is
21 an antiparasitic used to treat strongyloides and
22 onchocerciasis, which are worms, I think.

1 Anyway, there are lots of studies overseas:
2 India, Brazil, et cetera. The only thing that has been
3 studied in the United States is some case studies for
4 using it for scabies. It has been used overseas. Over
5 19 million doses have been used worldwide. It is a
6 pretty safe drug. In some countries, they just pass it
7 out on a regular basis to treat people for their worms.

8 The reason that they are using it overseas for
9 scabies in India and the other published studies was that
10 it was easier to use than the liquid formulations and
11 they had higher compliance.

12 The case studies from the United States are the
13 same thing. It has pretty good efficacy. It works 70 to
14 100 percent of the time with two doses to clear scabies.

15 It works very well for crusted scabies and people that
16 are resistant to repeated topical applications of
17 Permethrin. The main thing is that I don't know why we
18 would want to use an oral agent for scabies.

19 It has been used extensively in people over 15
20 kilograms. It is not indicated for pregnancy, but
21 overseas a lot of people use it and there has no fetal
22 toxicity or teratogens.

1 Let me see. I gave it a score of three
2 because, yes, there is no PK data on younger kids and
3 there is no efficacy data in the United States about
4 using it for scabies, but I don't think that is a high
5 priority to study. I just don't see why we need to have
6 an oral agent for scabies.

7 DR. WARD: Let's let Dr. Woods comment, and
8 then Dr. Epps.

9 **Secondary Review of Ivermectin**

10 **Dr. Charles R. Woods**

11 DR. WOODS: I think I would echo that largely,
12 except that I would like to see more data on this for
13 lice, maybe, even than scabies, which I think is a
14 potentially bigger problem for us in the end. So for
15 scabies maybe not, but I might give it a four.

16 It won't rank a high score in terms of
17 hospitalizations or chronic disease, but in terms of a
18 problem that is out there in pediatrics at least in terms
19 of perhaps growing resistance, there are difficulties
20 with lice. I would say it might be more useful there.
21 Scabies, maybe not. It would be nice to have as an
22 option but not necessarily a lot of further study for

1 that indication.

2 So I might give it a four in terms of score and
3 say we ought to look at it, but again, coming back for a
4 different indication, more for head lice as another
5 agent.

6 DR. WARD: Dr. Epps.

7 **Tertiary Review of Ivermectin**

8 **Dr. Roselyn E. Epps**

9 DR. EPPS: Good morning. As a pediatric
10 dermatologist, I can tell you we would need to study this
11 drug. I think it would be extremely helpful not only
12 because there are a lot of children. It is a school
13 problem. It goes through the schools and people who live
14 in crowded conditions. It goes around and around and
15 around. As a subspecialist, I am referred patients who
16 have had scabies for months and months and months. It is
17 very helpful for people who have atopic dermatitis or
18 skin problems who cannot tolerate topical preparations.

19 So a little bit more data would be very
20 helpful. Maybe it is not appropriate for infants, but
21 sometimes the infant has it, somebody holds the baby,
22 everybody holds the baby, everybody has scabies. So we

1 need some alternatives other than just topical Permethrin
2 and some of the topical sulfurs and some of the topical
3 things that don't work in people who are sensitive to and
4 cannot tolerate them.

5 DR. WARD: I knew nothing about Ivermectin, so
6 I found it interesting to read. The issue about
7 secondary infections in scabies appeared to me to be a
8 significant health problem in children. The difficulty
9 with compliance with topical treatment, I think, poses a
10 problem as well.

11 FDA Review of Ivermectin

12 Dr. Lisa L. Mathis

13 DR. MATHIS: I'm going to be the FDA
14 representative on this.

15 You may know that I discussed Lindane last
16 year. As we look at the indication of head lice, we have
17 multiple treatments for head lice. There are many
18 approved therapies and there is no problem getting
19 sponsors to come in to apply for new drug applications
20 for new drugs to treat head lice. We don't have a
21 problem.

22 In addition to that, head lice might be very

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1 annoying and something that we need to treat because it
2 does interfere with schooling, but it is not a public
3 health problem. Scabies is. If you look at parts of the
4 world, like third world countries where you don't have
5 adequate medical care, scabies accounts for a very large
6 percentage of the morbidity in children.

7 When we look at scabies in the United States
8 and we look at approved therapies, we have Permethrin,
9 which is actually very effective and is our first-line
10 therapy.

11 Outside of that, we have Crotamiton and
12 Lindane. Crotamiton has less than a 40 percent efficacy
13 rate, if you believe the current literature that is out
14 there, and there is resistance, documented resistance.
15 If you look at Lindane, it is a second-line therapy, so
16 if a patient fails Permethrin, they have to go to
17 Lindane. We know that there are problems with toxicity
18 with Lindane, especially in patients who may have
19 scratched their skin or have atopic dermatitis.

20 While we would rather see a topical formulation
21 for Ivermectin, we have to start looking at safer
22 alternatives for the treatment of scabies, and that is

1 why we strongly recommended that Ivermectin make the
2 list.

3 There have been a lot of patients in the world
4 that have used it, but most of them have been out in
5 Africa and there hasn't been very active surveillance of
6 safety. You only see what you look for, so when you hand
7 out the drug and then you disappear from the village, you
8 are not going to identify safety risks with the drug.

9 In addition to that, the doses that you need
10 for infestations are higher than what you need for river
11 blindness. It is also two doses. So we do need to
12 evaluate this drug for both safety and efficacy, and we
13 need safe alternatives for the treatment of scabies.

14 I can tell you -- perhaps somebody from the
15 division can comment -- we don't have sponsors knocking
16 on our doors with alternatives to treat scabies. It is a
17 condition of poor children who are living in crowded
18 conditions and there is not a lot of interest in it.
19 That is one reason why we think this would be a very good
20 thing to have studied.

21 **Open Discussion**

22 DR. WARD: Dr. Zito.

1 DR. ZITO: A question on its patent status.
2 This is off-patent?

3 DR. MATHIS: Yes, it is.

4 DR. WARD: Yes, Dr. Sachs.

5 DR. SACHS: If I can just add, in India for
6 example, 7 percent of all kids hospitalized for any
7 condition have scabies. So it really is a huge public
8 health problem.

9 I do want to mention that there was a recent
10 warning in MedWatch about difficulty in standing or
11 walking in toxic epidural necrosis.

12 DR. MATHIS: I should add, with Ivermectin,
13 too, everybody really does assume that it is a very safe
14 drug, but we have case reports in the New England Journal
15 of Medicine that actually talk about elderly patients who
16 are given oral Ivermectin for the treatment of scabies,
17 who ended up dying within several days because of
18 neurologic reasons.

19 DR. SACHS: I thought that was after six
20 months.

21 DR. MATHIS: Some of the cases were after six
22 months, some of them were very short-term. It does

1 attach to the P proteins, and so it increases the
2 permeability of the blood-brain barrier.

3 Actually, going to you, it has been used as an
4 adjunct. There are studies of it being used as an
5 adjunct to Baclofen for spasticity because it does hold
6 open those P proteins and increase permeability of the
7 blood-brain barrier.

8 So while we assume that it is a very safe drug,
9 and it is being used off-label for scabies, I think we
10 really need to assess the safety of it. Perhaps this
11 isn't going to be our safe alternative, but I think that
12 we need to determine that.

13 DR. WARD: Gary.

14 DR. OVERTURF: The other point is that it has
15 also been used in Filariasis prophylaxis as well. The
16 difference is that those prophylactic regimens use these
17 drugs very infrequently. I mean, the doses are much
18 lower, and you really can't extrapolate safety data from
19 many of the prophylaxis treatment regimens that are used
20 in Africa for what we might expect with scabies.

21 I personally think that it is overkill for most
22 scabies, but it is not a disease I see. I feel the same

1 way about lice. I think a lot of lice is overemphasized,
2 and I think a lot of the turmoil about issues about
3 resistance really don't appreciate the biology.

4 Regardless, if it is going to be used, safety
5 data really is, probably, needed.

6 DR. ZITO: I want to make the suggestion that
7 we think about, if we were to support additional research
8 here, that it be focused on safety, that we could think
9 about ideas like a registry or a protocol that shows that
10 the individual was resistant to safer alternatives as a
11 first step, and then a defined protocol in which safety
12 could be assessed.

13 DR. MATHIS: We actually would have to look at
14 efficacy as well to label it because we don't have any
15 efficacy data. So we always have to look at safety in
16 balance with efficacy.

17 DR. ZITO: What I'm alluding to is the fact
18 that the tradition of our trials has been that the safety
19 data is generally inadequate to answer many questions
20 because of a lack of standardization of the way the data
21 are collected, definitions, and what symptoms you would
22 look for. Also, because there has always been a sense of

1 under-reporting. You don't really go aggressively
2 looking for bad things when you are trying to demonstrate
3 effectiveness.

4 DR. WARD: I think that simply underscores the
5 need for careful study in which safety is collected
6 thoroughly.

7 MS. WOO: One thing that did come out in the
8 studies in the United States, all the cases in the case
9 studies were immunocompromised patients, and
10 immunocompromised patients who get scabies, it turns into
11 crusted scabies. This has been very effective in
12 clearing them up very quickly, but then you also have to
13 deal with safety with the immunocompromised patient, too.

14 DR. WARD: Dr. Epps.

15 DR. EPPS: Well, unfortunately, a lot of this
16 isn't reported because it is common or people recognize
17 it. They don't need to report it because when it is
18 diagnosed, quite simply, with oil and scraping, then you
19 move on and you treat everybody.

20 I will also say that there may be even more of
21 a public health issue when these people are admitted to
22 hospitals. There was a recent outbreak at a local adult

1 hospital -- not at our facility -- and these patients had
2 gone home and they had scabies and nobody realized it
3 until later. They had to call back and get the health
4 personnel treated.

5 So it is a problem. Of course, that is not
6 going to be part of their PR campaign, that you come in
7 and you get scabies, so people don't really talk about
8 it. They are embarrassed about it or they don't discuss
9 it, but it is not like having an ear infection.

10 DR. WARD: Steve.

11 DR. LAWLESS: We actually don't, obviously, see
12 much scabies in the ICU, but in the NICU, maybe.

13 [Laughter.]

14 DR. LAWLESS: The question I have, actually, is
15 on two things, just because it is new here and it is
16 getting intriguing here. If you treat it with this oral
17 medicine and you treat it for a certain period of time,
18 how long does it last in terms of the therapy? If you go
19 back to the living condition and you are being reexposed,
20 you are just going to be getting it back again. So you
21 are treating the public health matter of cleaning up the
22 area.

1 The second question is, is it in use right now?

2 I'm trying to do a tradeoff in my mind of one drug
3 versus another. You study it, it gets used, and now it
4 is actually sold as this is a new use for this drug and
5 expanding the market, versus a lot of drugs we are
6 looking at right now are already in use and we are trying
7 to decrease some morbidity that may be associated with
8 them.

9 So I have those two questions in terms of how
10 long does the effect last, and then, also, how big of a
11 market is there right now?

12 DR. MATHIS: Yesterday we were talking about
13 smoking cessation. A drug therapy isn't going to cure
14 the problem of overcrowding. It is not going to cure the
15 problem of poverty in the United States. So the drug
16 therapy has to be used in conjunction with other scabies
17 eradication programs.

18 That being said, a lot of patients do have
19 reinfestations. The problem is that then those patients
20 are identified as treatment failures and placed on
21 Lindane, where they have seizures.

22 So you are right, it is a big problem. I don't

1 know if any drug therapy is going to cure that, although
2 we do put this as part of a drug treatment program. In
3 some of the Lindane labeling, we actually go through
4 details about how to get rid of the scabies in clothing,
5 and head lice, too, since it is indicated for that as
6 well.

7 The other thing is, you are right, we may be
8 creating a new market for this drug, which then you have
9 to worry about safety, because you are going to increase
10 the use. When we look at the alternatives, Lindane is
11 safe and effective when used as labeled. The question
12 is, are people using it as labeled, because we are still
13 having serious reactions: seizures, death, even when
14 used as labeled.

15 So while you might increase safety concerns for
16 Ivermectin in itself, it may be relieving us of the
17 safety issues from Lindane or other alternative
18 therapies.

19 DR. WARD: Yes.

20 DR. ZITO: How much latitude in writing the
21 label do you have for it appearing as a second-line
22 treatment? What we did with Clozapine was indicate it

1 for treatment-resistant schizophrenia.

2 DR. MATHIS: I think that that would have to be
3 a review issue. If we found significant safety problems,
4 we would want to probably label it as a second-line
5 therapy. If, however, we didn't find significant safety
6 issues, I'm not sure why we would want to do that.

7 DR. WARD: Yes, Wayne.

8 DR. SNODGRASS: Related to that would be risk
9 of developing resistance for other therapies.

10 DR. MATHIS: That has always been a big concern
11 of ours. Now, there is documented scabies resistance to
12 both Lindane and Crotamiton, although there is no
13 documented resistance to Permethrin at this time.
14 However, bugs are a lot smarter than we are, and
15 eventually, I'm sure, they will figure that out and
16 develop a resistance.

17 Head lice, it depends on what part of the
18 country you are in, of course. I mean, head lice are
19 resistant to everything.

20 DR. WARD: On that note, why don't we go to
21 Malathion for lice, Dr. Snodgrass.

22 [Laughter.]

1 **Review of Malathion**

2 **Dr. Wayne R. Snodgrass**

3 DR. SNODGRASS: Malathion is an organophosphate
4 insecticide, and it is used in tonnage amounts in the
5 United States in agriculture and other similar uses.

6 I have a hard time recommending an AK-47 for
7 lice. In the labeling, it is under age 12, I believe.
8 Maybe it is age six.

9 PARTICIPANT: Greater than six.

10 DR. SNODGRASS: Six, maybe it is.
11 Manufacturers do not recommend it, and there are concerns
12 about increased skin absorption in young infants.

13 It is an organophosphate. I guess I'm coming
14 from a different spectrum, but I treat those kind of
15 poisonings. So to create them I think would be a
16 problem. You would have to be in a position to say if
17 you are going to study this drug in young infants that
18 you are going to monitor cholinesterase and look for some
19 adverse effect there.

20 This then gets back to, well, it is head lice.

21 How do you deal with head lice. When we talk about
22 resistance, how is resistance measured, and what about

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1 mechanical methods. That gets into motivation, and there
2 are all the issues about setting and social setting and
3 all this.

4 So I don't think this has a good safety profile
5 to recommend it be studied.

6 DR. WARD: Ms. Woo?

7 **Secondary Review of Malathion**

8 **Teri Moser Woo**

9 MS. WOO: Once again, I saw this as one of my
10 drugs, and I was like, "What is this? Why are we using
11 Malathion again?" I thought that was like an old thing.
12 It went off the market and it came back on.

13 I was here last week for another pediatric
14 pharm meeting and talked to a pediatrician from Tennessee
15 who said they use it all the time for head lice in
16 Tennessee. So I guess this isn't such a dead issue.

17 PARTICIPANT: No pun intended.

18 [Laughter.]

19 MS. WOO: It is a little scary to me to be
20 using an organophosphate. There is no PK or PD data for
21 children under age five. There are real concerns about
22 toxicity in infants and young children.

1 There are many studies showing efficacy. It
2 works really well. It is like 100 percent effective
3 against lice. It is really great stuff. It is over-the-
4 counter in the United Kingdom. You can go down to your
5 local drugstore and buy it and use it there without any
6 concerns for safety there.

7 My big concern is just toxicity in young kids.

8 So if we have all this resistance in lice and people are
9 out there using it, I would give it a three on the
10 scoring sheet, but the problem is, if people are using
11 it, we really do need safety data for the younger kids.
12 People just use it for everybody in their family, even if
13 the label says under age five not to use it.

14 **FDA Review of Malathion**

15 **Dr. Lisa L. Mathis**

16 DR. MATHIS: I would almost say ditto to my
17 Ivermectin comments. Again, when we look at the safety
18 of this drug compared to the safety of Lindane, it is an
19 organophosphate, so we do have to be careful about
20 checking acetylcholinesterase levels in the blood, that
21 and our PK/PD, especially when you are talking about
22 scabies, which is from the neck down, rather than head

1 lice, which is just on the head. Again, head lice isn't
2 really our big concern. Scabies is.

3 So the studies would definitely have to
4 demonstrate no systemic toxicity, and I'm sure Dr. Epps
5 can give you a good lecture that the fact that it is
6 topical doesn't mean that it is not absorbed and seen by
7 your body. All these drugs are absorbed, and we do have
8 to worry about systemic toxicity.

9 **Open Discussion**

10 DR. LASKY: I also wanted to throw out that we
11 have visited some of these issues because Lindane was on
12 our first list. We have struggled with the issues around
13 Lindane, and one of the issues is, well, if you take this
14 off or you limit its use further, what will you use
15 instead. I think later this afternoon it will be
16 interesting to talk about the issue of groups of drugs --
17 and these really suggest themselves -- Lindane,
18 Ivermectin, and Malathion, that really would have to be
19 studied together or in context of each other because the
20 use is related.

21 DR. WARD: Stan?

22 DR. GROGG: There may be two mechanisms of

1 action on this medication. One is the pesticide
2 activity, but the second, it is flammable. So if you put
3 it on and you light a cigarette, it may take care of the
4 head lice.

5 I think they are phase 3 studies, but occlusive
6 dressings that are coming out that should be available
7 soon for head lice that basically suffocate the head
8 lice, like the old mayonnaise that we have used
9 frequently in the pediatric practice.

10 So I think there are going to be some new
11 things available for head lice avoid the toxicity of
12 medications.

13 DR. MATHIS: But I do want to emphasize that we
14 are not discussing the indication of head lice. Remember
15 that scabies is under the stratum corneum and you can't
16 suffocate it like you can head lice. It is already
17 approved for use in head lice.

18 DR. LASKY: But not under age five.

19 DR. MATHIS: That is correct.

20 DR. WARD: So I assume that the real issue is
21 five and under, do we feel this needs to be studied in
22 the young child to determine just how much it takes to

1 cause them to seize.

2 DR. MATHIS: Well, yes. You would have to have
3 greater than 50 percent of cholinesterase inhibition to
4 start seeing seizures, so that is probably -- uh oh, Dr.
5 Snodgrass is going to get me for that.

6 DR. SNODGRASS: No, no, no. You're right, if
7 it is used according to the directions. The problem with
8 Lindane is it doesn't get used according to the
9 directions. That is going to happen here as well, no
10 matter what you try to do. That is where the problem
11 comes in. They reuse it, they pour on 10 times as much.
12 They keep using it for several days in a row, never wash
13 it off, and all those issues come up. That is where you
14 begin to get into trouble.

15 DR. WARD: Dr. Sachs.

16 DR. SACHS: The other thing is, again, head
17 lice is very common. Up to 30 percent of kids get
18 infected. I can tell you in my practice it was the
19 number one after-hours call. People freak out when they
20 get diagnosed with head lice.

21 In a nice study of prevalence, they found that
22 there are a lot of prescriptions written for this

1 product. Malathion and Permethrin were the top products.

2 In some comparative studies, it looks like Malathion may
3 have less resistance than the Permethrins and Lindane, so
4 there may be that potential benefit. The adverse events
5 certainly can't be understated.

6 DR. WARD: Granted it will probably be misused,
7 as you said, Wayne. So in an epidemiological sense, what
8 is the frequency of significance AEs with Malathion?

9 DR. MATHIS: There is a pretty low rate of
10 reported AEs, and there is a very low rate in the
11 clinical studies that were performed for the approval as
12 well. I mean, it appears to actually be very safe when
13 used as labeled.

14 DR. SACHS: I found 12 adverse events in the
15 database, 12 since this was approved, and it looks like
16 the prescriptions written, it said the prevalence was
17 like 12.1 per 1,000 affected kids.

18 DR. MATHIS: Dr. Sachs, correct me if I'm
19 wrong. All 12 of those weren't in pediatric patients, is
20 that correct?

21 DR. SACHS: No, I looked just for pedes.

22 DR. MATHIS: You did, okay.

1 DR. SACHS: They may be duplicates. I didn't
2 actually analyze them further.

3 DR. MATHIS: Were they severe? I mean, some
4 people actually report treatment failure as an adverse
5 event.

6 DR. SACHS: It was mixed.

7 DR. MATHIS: It was mixed.

8 DR. SACHS: And a very superficial look at the
9 adverse events.

10 DR. ZITO: Could we just get a little
11 clarification on that? How many years since marketing
12 experience is represented by that data?

13 DR. SACHS: Since approval.

14 DR. MATHIS: That was in the early '80s, so it
15 is over 20 years.

16 DR. ZITO: And we are aware of the great under-
17 reporting?

18 DR. MATHIS: Absolutely. In the best of
19 situations, we see about 10 percent. That is the number
20 that is thrown around.

21 DR. ZITO: In the literature, all I found was
22 allergy and respiratory NI symptoms, in addition to what

1 was in the label.

2 DR. SNODGRASS: It seems that head lice and
3 perhaps scabies are prime candidates for new mechanisms
4 of action for new agents that have a better safety
5 profile. That is a longer term goal.

6 DR. MATHIS: Dr. Snodgrass, if you know of any
7 of those, encourage those sponsors to come in.

8 DR. SNODGRASS: And all of the economic issues.

9 DR. LASKY: It is a money-maker, so actually,
10 we hear there are quite a few drugs out there, I mean,
11 over-the-counter, so this should be an incentive.

12 MS. WOO: I had one mom tell me she spent \$150
13 trying to get rid of the head lice. I'm like, "What did
14 you buy?" She went and bought everything off the shelf.

15 I mean, the one thing about having prescription
16 medicines is we really do control the amount that they
17 get, and it is a much more controlled situation, but the
18 over-the-counter medicines can't hurt them.

19 DR. LASKY: We had a talk on Lindane and
20 someone came in with a slide showing about 20 feet of the
21 over-the-counter aisle for lice preparations.

22 DR. MATHIS: And again, alternatives for head

1 lice treatment are not a problem. We have sponsors
2 coming in regularly with head lice treatments. The
3 problem is scabies. I don't know when the last time was
4 that we had an application submitted for a scabies
5 treatment.

6 MS. WOO: The information I got was that this
7 was for lice. Are we talking about using Malathion for
8 scabies now?

9 DR. MATHIS: I think that if it is on the list
10 for head lice, we have to look at it for that. You're
11 right.

12 DR. WARD: You can write in "for scabies."

13 [Laughter.]

14 DR. WARD: It can be advice to the agency.

15 Yes.

16 DR. ZITO: This is not the venue, but I hear a
17 call for people to go back to their various associations
18 and to argue for better education around these issues.

19 DR. WARD: If there is no more discussion, we
20 are going to move to a group of dermatologic drugs, or
21 some related, some topical steroids. We will try to deal
22 with all those together, I believe, before we go for a

1 break.

2 We will start with Aclometasone dipropionate
3 cream for dermatitis.

4 Dr. Epps.

5 DR. EPPS: I will talk about all the topical
6 steroids together, if that is okay. Fortunately, in
7 dermatology, we have progressed beyond "if it is dry,
8 make it wet; if it is wet, make it dry."

9 DR. WARD: I have to go back to school, then.

10 [Laughter.]

11 **Review of Aclometasone Dipropionate Cream for Dermatitis,**
12 **Desonide Ointment for Dermatitis, and Hydrocortisone**
13 **Valerate Ointment and Cream for Dermatitis**

14 **Dr. Roselyn E. Epps**

15 [PowerPoint presentation.]

16 DR. EPPS: Topical corticosteroids have been
17 available since the 1950s, so they have been around for
18 about 50 years. They are widely used in pediatric
19 dermatology, and they are generally safe if used as
20 directed, but we will talk a little bit more about them.

21 They are frequently used in pediatric
22 dermatology practice for many dermatoses. The most

1 common examples would be atopic dermatitis, or eczema,
2 contact dermatitis, seborrheic dermatitis, and psoriasis.

3 Atopic dermatitis and psoriasis bear special mention
4 because they have early onset. Atopic dermatitis
5 frequently presents in the newborn period. Some people
6 will say the patient was born with eczema, just popped
7 out with eczema, but they are chronic and they are
8 recurrent.

9 Atopic dermatitis, the prevalence has been
10 increasing over the last few years or decades. In the
11 1970s, they said perhaps, maybe, 1 to 3 percent. It has
12 increased over the decades, and it is now estimated
13 perhaps as many as 20 percent of American children are
14 affected.

15 Now, perhaps the numbers were higher before.
16 Perhaps the reporting is better. Fortunately, in atopic
17 dermatitis, with age the prevalence decreases. They are
18 pretty equal as far as gender is concerned. You will
19 find some differences between different countries or
20 nationalities, but generally, it is quite prevalent in
21 the United States.

22 Psoriasis is another condition that we do see,

1 which has more of a bimodal peak as far as prevalence, or
2 onset, I should say, in childhood and in adult
3 populations. Psoriasis prevalence in children is thought
4 to be perhaps 4 to 5 percent. You may hear higher
5 numbers. Contact dermatitis, the prototype is, say,
6 poison ivy, nickel dermatitis, other more limited
7 conditions. Seborrheic dermatitis we often see in the
8 newborn period as cradle cap, but we also see it in other
9 children as well.

10 The effects of topical corticosteroids are
11 anti-inflammatory, antipyretic, as well as
12 vasoconstriction. The vasoconstriction that can occur is
13 the basis for a lot of the studies of potency which we
14 will discuss.

15 The mechanism of action is thought to induce
16 lipocortins, which is a group of proteins which inhibit
17 phospholipase A2, and consequently, because of increasing
18 levels of arachidonic acid, it affects inflammatory
19 mediators such as the prostaglandins and leukotrienes.
20 So that is the current thinking as far as the mechanism
21 of action for topical corticosteroids.

22 Biochemically, they are bound to plasma

1 proteins, are metabolized primarily in the liver, and are
2 excreted by the liver into the bile, as well as by the
3 kidney.

4 When using topical corticosteroid, there are
5 several patient factors to consider. One, of course, is
6 patient age. You wouldn't use a super-potent steroid in
7 a young infant or a small child. The body surface areas
8 involved, you must consider that, the body site that is
9 being treated. Different parts of the body or different
10 skin areas have different thicknesses, for example. The
11 thinner areas would include the eyelids, the groin area,
12 face, whereas thicker areas would include the palms and
13 soles as well as other parts of the body.

14 It is also important to consider the condition
15 that is being treated. Some respond better to more
16 potent or milder corticosteroids. The skin integrity is
17 important, whether or not there are excoriations or open
18 areas that can increase the absorption. Skin type and
19 pigmentation can also be a factor because with people of
20 color or darker pigmentation, sometimes it can result in
21 hypopigmentation as a side effect.

22 When considering the medication, you consider

1 the potency; the vehicle -- which means whether it is an
2 ointment or a cream. We will talk more about potency and
3 vehicle -- the application method; the frequency of
4 application, whether it is once a day, twice, three times
5 a day; the amount of product that is being applied; as
6 well as the treatment duration, whether it is days or
7 weeks or months.

8 Now, when considering the potency, they are
9 classified according to vasoconstriction studies. The
10 original studies were done in the '60s. There have been
11 some later studies along the way as new medications
12 develop and as the process for determining
13 vasoconstriction has been modified.

14 Class 1 is super-potent. An example of that
15 would be Clobetasol. Class 7 would be an over-the-
16 counter corticosteroid, CortAid or your hydrocortisone.
17 Most of the others also fall in between.

18 Now, regarding the vehicle, the ointment,
19 cream, lotion, gel, solution, and foams are available for
20 topical corticosteroids. The potency within a particular
21 class can depend on which preparation you use. For
22 example, most people consider ointment to be a little bit

1 stronger than the cream, which is stronger than the
2 lotion, although that is not always the case.

3 Various concentrations of an active agent
4 within a similar vehicle doesn't result in a different
5 vasoconstrictor assay. In other words, 0.5 percent and
6 0.01 percent for the same chemical may be the same
7 strength vasoconstriction in the same vehicle, in the
8 same cream. It is also important to notice that all
9 vehicles are not created equally, and we will talk a
10 little more about that, too.

11 Now, what are the local side effects we see.
12 In order of frequency, we see itching, irritation,
13 dryness. Folliculitis can occur as a side effect of
14 topical corticosteroids. Hypertrichosis, particularly
15 with the stronger ones or fluorinated ones. Acneiform
16 eruptions, hypopigmentation. We do see perioral
17 dermatitis when it is used on the face.

18 Allergic contact dermatitis can occur. That
19 does bear special mention. Some people are actually
20 allergic to the active agent, the steroid.

21 Some people are actually allergic to something
22 in the vehicle. In other words, some of the creams, for

1 example, have preservatives such as parabens,
2 particularly in over-the-counter medications. Some of
3 them are allergic to tixocortolpivalate, which is in a
4 lot of hydrocortisones. There is a whole family of
5 preservatives and emulsifiers and things that people can
6 develop contact sensitivity to.

7 Also, if you are allergic to a topical
8 corticosteroid, there are groups A, B, C, and D,
9 according to the contact dermatitis people, where you may
10 cross-react within a particular category. So sometimes
11 the treatment isn't helpful.

12 There may also be maceration or secondary
13 infection, which would include bacterial and fungal and
14 viral infections. Not only your typical bacteria, but
15 also more unusual ones. The viral would be molluscum and
16 HPV, as well as candida and other fungals. Atrophy and
17 striae are the ones that most people become very
18 concerned about. Obviously, they are much lower as far
19 as incidence is concerned, but atrophy can be reversible.
20 Striae are not.

21 The systemic side effects are what we become a
22 little bit more concerned about. You can see

1 hypothalamic pituitary axis depression, adrenal axis
2 suppression, Cushing Syndrome, as well as linear growth
3 retardation.

4 Last year, the Dermatologic and Ophthalmic Drug
5 Advisory Committee held a whole-day meeting concerning
6 topical corticosteroids and their possible side effects.

7 Some of the results we will be talking about in the next
8 few slides.

9 So as far as the HPA axis suppression, which I
10 consider to be the most significant, adrenal suppression
11 occurred with systemic absorption of the drug. This is
12 particularly true of more potent varieties as well as
13 people who applied it to large surface areas. The
14 suppression occurred not only with the higher class but
15 also the lower classes, which might be the four or the
16 five, even when used properly sometimes.

17 I alluded to the surface area, which
18 contributed. Some patients were applying it head to toe.

19 A little is good, a lot is better, so they applied it
20 everywhere. But the axis suppression was usually
21 reversible within 14 days. A lot of these were performed
22 by stimulation tests to assess that.

1 The HPA axis suppression occurred with routine
2 use at times. Those children are at risk for adrenal
3 crisis. Now, minor HPA axis suppression can occur. We
4 don't really know what the clinical significance of that
5 is, whether they respond under stress or not. It is hard
6 to know. A lot of people don't think about it, so it is
7 probably under-recognized and under-reported. You only
8 see the people who crash, unfortunately.

9 Now, today we are considering Aclometasone --
10 there is an extra L according to the insert --
11 dipropionate, Desonide, as well as Hydrocortisone
12 valerate and the studies that were done.

13 Now, Aclometasone, there is no specific data as
14 far as pediatric -- oh, I'm sorry, as far as how
15 frequently they used it. They had some Express Scripts
16 data which was relayed to me this year. So it may not be
17 from 2004, but that is when I received it.

18 Desonide. There are 0.4 prescriptions per 100
19 children enrolled, whereas for Hydrocortisone of all
20 types -- we will talk about the family of Hydrocortisone
21 topical applications -- there are 1.62 prescriptions. So
22 at least 2 percent of the children enrolled with Express

1 Scripts received at least two of these drugs, and perhaps
2 more when you include the Aclometasone.

3 Now, Aclometasone goes by the trade name of
4 Aclovate. There is a generic. It is generally prepared
5 as a cream or an ointment and 0.05 percent strength. It
6 is a synthetic corticosteroid, and it is mild. It is
7 group 6, so it is a little bit, as I tell patients, above
8 the drugstore, which is a seven.

9 It is approved for patients over one year of
10 age, according to the insert of GlaxoSmithKline. Safety
11 and efficacy in use over three weeks had not been
12 established, which means it hadn't necessarily been
13 tested according to them. It is not recommended over a
14 large body surface area of 20 percent, and it is useful
15 for most dermatoses.

16 Now, there were several clinical trials that
17 had been indicated. There was an open study of healthy
18 volunteers. Thirty grams of cream were applied to 80
19 percent of the body surface area twice a day, so that is
20 60 grams of cream. Then, in addition, they put on a
21 plastic suit to provide occlusion for 12 hours a day, and
22 no HPA axis suppression occurred, so that is pretty

1 useful data. Although it doesn't translate to
2 pediatrics, certainly that is a significant amount of
3 medication over a period of time.

4 A second study was a randomized control trial
5 comparing Aclometasone and Hydrocortisone 1 percent
6 ointment in children with eczema, both in the ointment
7 form. It was applied twice a day for three weeks. No
8 telangietasias or atrophy were seen, and they were
9 equally effective.

10 Most of the clinical trials are done with
11 ointment because then you eliminate those compounding
12 factors of the vehicle. Now, there are some that are
13 coming up with creams, but most of the time ointments
14 were utilized.

15 In another randomized double blind control
16 trial, there were 33 psoriasis patients, which is a
17 little bit different than the atopic dermatitis, where
18 the Aclometasone and Desonide were applied twice a day
19 for three weeks. Rapid improvement was seen, and there
20 was no statistical difference between the two. So that
21 was useful as well and flows into our discussion of
22 Desonide.

1 Its trade name is Desowen. Another company,
2 Fougere, has also sold or manufactured Desonide. It
3 comes as a cream, ointment, and a lotion. It is a non-
4 fluorinated corticosteroid, which is very helpful, and it
5 is also of a mild potency.

6 The safety profile has been looked at. In a
7 particular study that came out this year, the Adverse
8 Event Report Database was surveyed, as well as trials
9 published regarding the cream, ointment, and the lotion.

10 The data was collected from 1992 in all countries where
11 the drug was available.

12 Now, only 62 adverse event reports were made.
13 They were primarily consumers. I am sure this is more of
14 a tip-of-the-iceberg phenomenon. A lot of times when
15 something doesn't work or there is irritation, they don't
16 use it anymore and they throw it away, and it is not
17 reported. They were local reactions, but none was
18 serious.

19 As far as HPA axis suppression has been
20 evaluated regarding Desonide, this was specifically for
21 children with atopic dermatitis and was randomized and
22 controlled, comparing Desonide and Hydrocortisone

1 ointments for four weeks. No HPA suppression occurred
2 for either group.

3 Next, there was a randomized double blind
4 right/left study, which means one cream was put on the
5 right side and the other is put on the left side on the
6 same patient. They compared Desonide but at different
7 strengths, one with a 0.05 percent and one with a 0.1
8 percent. There were 40 patients hand eczema, and there
9 was no statistical difference in the vasoconstriction or
10 the clinical responses. So that would go along with
11 different concentrations within the same vehicle.

12 A multi-center randomized investigator-masked
13 parallels group study was also performed with Desonide
14 compared to Hydrocortisone, 1 percent ointments, twice a
15 day for five weeks, and in a small subgroup up to six
16 months. There were 113 children enrolled, which is a
17 good size study for pediatric evaluation. The Desonide,
18 as one would expect, had greater efficacy, more rapid
19 response, but was equally safe.

20 Next was a randomized double blind study
21 comparing Desonide cream versus Betamethasone valerate
22 cream, which was a predecessor. It is halogenated, but

1 it is still of the same class. Patients ranged from one
2 to 80 years. I didn't see specifically how many children
3 were in the pediatric group, but they didn't see side
4 effects of clinical significance. This was an older
5 study, 30 years old.

6 Now, regarding Hydrocortisone, which many of
7 the drugs were compared to, there are different
8 structural analogs. Some people or clinicians don't
9 always realize that there are different strengths, even
10 though they all say "Hydrocortisone." So sometimes the
11 Hydrocortisone is methylated, halogenated, hydroxylated.

12 Oxidation can occur, which is dehydrogenation -- this is
13 basic chemistry -- esterified, and if there is a glycol
14 group present, acetamide form can be formulated.

15 Now, how does that affect the strength. Well,
16 Hydrocortisone valerate ointment, which is what we are
17 talking about today, is considered a class 4, whereas the
18 Hydrocortisone valerate cream is class 5.
19 Hydroxycortisone buterate ointment and cream are class 5,
20 whereas the lotion is class 6. So it drops down as far
21 as vasoconstriction studies are concerned. The
22 Hydrocortisone 1 percent, on which most of the trials

1 were done or compared to, is a class 7. So different
2 potencies within the same family.

3 Now, some people or some practitioners will
4 prescribe the 0.2 percent, thinking that that is weaker
5 than the Hydrocortisone 1 percent because the percentage
6 is a different number. Patients often make that mistake
7 as well. In fact, the Hydrocortisone valerate is
8 actually mid-potency Hydrocortisone.

9 So the brand name is Westcort. It is cream and
10 ointment in form. It is not fluorinated and synthetic.
11 As I stated before, the ointment is a class 4 and the
12 cream is a class 5.

13 Unfortunately, the studies in Hydrocortisone
14 valerate were extremely limited. This one is from 1978,
15 which was a randomized double blind bilateral paired
16 study which compared Betamethasone valerate and
17 Hydrocortisone cream and placebo against Hydrocortisone
18 valerate. Twenty-five of the 68 patients were under 14
19 years. They all had chronic atopic dermatitis, and a
20 four-week trial was undertaken.

21 The Hydrocortisone valerate was equal to the
22 Betamethasone valerate but of course superior to

1 Hydrocortisone and placebo.

2 In another multi-center randomized evaluated
3 blind and parallel group trial, Hydrocortisone valerate
4 cream was compared to the Mometasone furoate cream, 0.1
5 percent -- for those of you who are wondering, that is
6 Elocon, which is a group 4 potency -- once a day for
7 three weeks. They had 219 pediatric patients, and the
8 Mometasone was superior to Hydrocortisone valerate cream.

9 It was also indicated on the paper that it was
10 under a generous grant from Sharing Plow [ph], so you
11 have to take that into consideration for this multi-
12 center group. Consider the source.

13 So topical corticosteroids are widely used in
14 pediatric dermatology. They are generally safe. There
15 was no documented HP axis suppression for Aclometasone,
16 Desonide, or even Hydrocortisone 2.5 percent, but there
17 were very limited studies regarding Hydrocortisone
18 valerate, particularly in the age group where the onset
19 occurs.

20 Using the evaluation list, I would give it
21 perhaps a 3.0 to a 3.5. I think where data might be
22 helpful would be in patients under one year old, where we

1 frequently have the onset. I think although patients are
2 not frequently hospitalized, when they are hospitalized,
3 they are hospitalized because they are superinfected and
4 bacteremic or they have eczema herpaticum, where you have
5 herpes infection on top of the eczema. That is pretty
6 serious. It can be quite a threatening infection.

7 Although there is not high mortality, the
8 prevalence is huge and increasing. I think there are a
9 lot of studies as far as Aclometasone and Desonide but
10 not as many in Hydrocortisone valerate. That may be
11 useful as far as HPA axis suppression is concerned. I
12 think there is a lot of hesitancy not only in the medical
13 community but also in the population about steroids.
14 Everyone thinks that they are equal and that you are
15 going to grow a beard and run a marathon, when in fact,
16 as I said, they have been around for 50 years.

17 I think a little bit more data as far as
18 suppression is concerned would be helpful, especially
19 since we are finding that this is a class 4 and some of
20 the suppression occurred in similar populations.
21 Certainly, there are plenty of patients out there to test
22 it for.

1 I don't know if there are any questions.

2 DR. WARD: Before we have some secondary
3 presentations, in your clinical practice, is there an age
4 range, for example six months or one month, in whom you
5 would only use, for example, 1 percent Hydrocortisone and
6 you wouldn't use a class 4 level of potency?

7 DR. EPPS: Well, usually, by the time they have
8 come to me, something has already been put on them and
9 they are beyond the drugstore.

10 I usually don't jump that high. I mean, there
11 are 20, 30 different topical corticosteroids out there.
12 I might use something mild within the same class. I tend
13 to emphasize more topical care issues, avoidance issues,
14 but there are some people who use it very sparingly and
15 there are some who use it as a moisturizer.

16 I think if we had a little bit more data, maybe
17 it would be reassuring, or at least we would have a
18 little bit more information that could be helpful.
19 Certainly, I don't jump to potent ones because of the
20 ratio of the body surface area to the weight. You can't
21 safely use a potent steroid in a young baby.

22 Also, I meant to mention, the diaper area is

1 particularly problematic because the diaper effectively
2 creates occlusion. When you have the moist environment
3 which is occluded, the absorption is much higher. So
4 sometimes that is a problem as far as diaper dermatitis
5 is concerned. Those patients are particularly much more
6 likely to have absorption and the systemic side effects
7 because of the occlusion of the diaper and the moist,
8 warm environment.

9 DR. WARD: Dr. Winer, did you want to make some
10 remarks?

11 **Secondary Review of Acclometasone Dipropionate and**
12 **Desonide Ointment for Dermatitis**

13 **Dr. Karen K. Winer**

14 DR. WINER: Basically, looking at the data that
15 was provided, I came to the conclusion that overall the
16 topical glucocorticoids in the lower dose is probably
17 generally safe in adults. However, it looks like in
18 children we don't have the data to say it is safe in the
19 very young kids.

20 As an endocrinologist, I'm not only looking at
21 adrenal suppression, I think that there are other issues
22 that have not been addressed in any of the studies that

1 have been done to date. First of all, it is linear
2 growth, which goes along with adrenal suppression, HPA
3 axis suppression, and also impairment of bone accrual,
4 which no one mentions at all.

5 I would say, if there is an impairment of
6 growth, there is probably an impairment of bone accrual
7 as well, so I think that those three things, not just the
8 HPA axis, are very, very important in growing children
9 and have not been adequately addressed so far.

10 It is interesting; I just in general did a
11 search on eczema, and I noticed that there are several
12 reports that kids with eczema or chronic eczema are
13 generally shorter. One report said that 22 percent of
14 children with eczema have a height of less than the third
15 percentile. So one would conclude that these
16 glucocorticoids that are used on a chronic basis are
17 having a systemic effect.

18 I thought it was interesting that a lot of the
19 data that was provided was on a very small number of
20 kids, so it is really hard to really come to a
21 conclusion.

22 In the Aclometasone, as Dr. Epps mentioned,

1 there was one study in 28 kids that said there was
2 basically no effect on the HPA axis. However, you have
3 to look at how these studies are done. Some people look
4 at just the plasma A and plasma cortisol and some, I
5 think, do it correctly, where they are actually looking
6 at the HPA axis by doing a chlorotyrosine stimulation
7 test.

8 I think there was only one that I could find,
9 or two, actually, that used the chlorotyrosine
10 stimulation test. They both were not in the packet. One
11 was by Tom Moshang in CHOP [ph.]

12 It is interesting; the largest study, that
13 multi-center study of over 100 kids, Bowman, Gray, and
14 Baylor, they didn't even look at the HPA axis. They
15 didn't measure the kids' heights or weights. They just
16 looked at the lesions. So to say that it is safe and
17 there is no systemic effect, if you are not even
18 measuring these things, it is really hard to really come
19 to any conclusion.

20 As far as the actual FDA-approved label, I
21 think it is appropriate. It provides the warnings that I
22 think should be there. However, the Aclovate, I didn't

1 understand why they chose one year as the cut-off. They
2 say in children over one year old. I assume it is
3 because of the kids less than one year are in diapers,
4 but kids greater than one year are also in diapers.

5 So the studies have not been done, and it is
6 really hard to say that kids greater than one year can
7 use these drugs with caution and kids under one year
8 cannot. So that is, I think, just a very arbitrary cut-
9 off in the label for Aclovate.

10 Pretty much, the labeling is all the same. I
11 think the data that they are citing is by Monroe and the
12 1970s studies. It is old data, and one wonders about the
13 validity of that data now that we have better assays
14 available to us and better ways to ascertain adrenal
15 insufficiency.

16 So I agree. I think I would score it a three.

17 We need more studies in this area. It is a very
18 prevalent disease, and it is not just adrenal suppression
19 which can cause death given certain circumstances.
20 Adrenal suppression is not really reversible quickly. I
21 mean, it is reversible in many of these studies because
22 it is given to these individuals for less than a month.

1 However, if the child is taking steroids for one, two,
2 three years, they will have adrenal suppression after you
3 stop the drug for as long as one year. So that is a very
4 dangerous situation, especially if the physician doesn't
5 know about it and there is no Hydrocortisone therapy
6 given to that child.

7 So I think basically more studies should be
8 done in this area.

9 DR. WARD: Let me push you on that aspect.
10 Should all age ranges of children be studied, or is it
11 particularly under a year of age?

12 DR. WINER: I think all age ranges, simply
13 because we are not just dealing with adrenal suppression.
14 I think adrenal suppression is very important, but we
15 are talking about linear growth and we are talking about
16 bone accrual. I think that even in the adolescent age or
17 in the school age, those are very important issues. It
18 just has not been measured at all.

19 DR. WARD: Dr. Epps, I want to ask you, we have
20 been trying to assign a degree of rating that we feel
21 would be appropriate with respect to whether it needs to
22 be studied or not, low being not much need, up to 10,

1 needing study. Would you commit yourself?

2 DR. EPPS: Well, I certainly feel that there is
3 a need. I would say perhaps maybe a six or a seven is
4 reasonable. Generally, they are pretty safe. Honestly,
5 I don't see that many side effects with this group, but
6 as she has pointed out, there can be systemic side
7 effects.

8 These are chronic diseases. I mean, there are
9 people who have atopic dermatitis their entire life. It
10 is not something that is just going to go away. The same
11 is true for psoriasis, and I guess some people believe
12 that they react differently, different conditions respond
13 differently to different medications. So certainly, you
14 could start with atopic dermatitis. There is a huge
15 population.

16 I guess, certainly in my population in my
17 practice, it is pretty important. I know in the scheme
18 of things this isn't malignancy, but it is important.

19 DR. MEYTHALER: Which one of the three would
20 you choose?

21 DR. EPPS: Hydrocortisone valerate. I mean, it
22 is very sparse, and it is old. I mean, the studies are

1 almost 30 years.

2 DR. MEYTHALER: Yes, but it is also, you said,
3 the one that is used the most frequently.

4 DR. EPPS: Correct. So you want to test that.
5 And it is the strongest. The potency is the highest.

6 DR. NIKHAR: Can I say a few words, please?

7 DR. WARD: Please.

8 **FDA Review of Aclometasone Dipropionate, Desonide**
9 **Ointment for Dermatitis, and Hydrocortisone Valerate**
10 **Ointment and Cream for Dermatitis**

11 **Dr. Bindi Nikhar**

12 DR. NIKHAR: I'm Bindi Nikhar from the Division
13 of Derm and Dental Products at the agency. I heard Dr.
14 Epps' talk, and generally we agree with most of what Dr.
15 Epps had to say, and what Dr. Winer pointed out.

16 Dr. Winer pointed out about growth studies and
17 so on in children. I think the division has debated
18 about whether growth should be looked at in children,
19 especially when they have been on topical
20 corticosteroids.

21 Unlike the studies that were done in children
22 involving inhaled steroids and steroids for the nasal

1 preparations, in children it becomes somewhat difficult
2 because it is atopic dermatitis. Chemical cause can wax
3 and wane, and children who don't improve then go on to
4 stronger steroids. So it is difficult to basically have
5 them on that same agent for a long period of time.

6 We do realize that growth is a very sensitive
7 indicator. Sometimes growth can be suppressed without
8 actually having HPA axis suppression, but I think that is
9 something that is within the consideration of the
10 division.

11 I also wanted to point out that Hydrocortisone
12 acetate, the class 7 steroid that is available over the
13 counter, we actually have concerns about that because
14 there are no pediatric HPA axis suppression studies on
15 Hydrocortisone acetate. Actually, what we were going to
16 propose was that this drug should be studied and this
17 drug should be incorporated on the list.

18 In fact, I was going to talk about that, but
19 this is widely used. It is available over the counter.
20 It was originally marketed as a prescription drug in
21 1952, and the agency classified it as being generally
22 safe and effective in the OTC monograph in 1983. Right

1 now, there are three concentrations, the 0.25, the 0.5,
2 and the 1 percent concentration.

3 It can be used three to four times daily by
4 adults and children over two years of age, and the label
5 just indicates warnings directing consumers to stop use
6 if symptoms get worse or last longer, and that children
7 less than two years of age should not use it.

8 In 1973, based on the insulin stress test in
9 adult patients, it was deemed that there was an HPA axis
10 suppression, but of course, a cortisone stimulation test
11 was not used, and the division uses that test for
12 assessing HPA axis suppression now.

13 We have concern there could be prolonged
14 periods of use, including the diaper area and, of course,
15 under occlusion. So we think it would be in the interest
16 of public health to actually study Hydrocortisone acetate
17 1 percent in pediatric patients. The current safety
18 information is very limited about this drug.

19 **Open Discussion**

20 DR. WARD: Why wasn't that on the list?
21 Seriously. I mean, there has been a big process to
22 obtain information to make this as relevant as possible.

1 DR. NIKHAR: Sure.

2 DR. WARD: We have three fairly potent products
3 on here, and if the least potent one available over the
4 counter is the one that the division feels we should
5 study --

6 DR. NIKHAR: Actually, I would like to point
7 out that the sponsors who would like to take their
8 topical corticosteroid products over the counter, they
9 are compared to Hydrocortisone acetate when, actually, we
10 have no suppression studies.

11 DR. WARD: Gee, I think we can get those
12 studies done.

13 DR. LASKY: The drugs came to us in a large
14 group, and we winnowed them down. We did consult with
15 the division, and we did have FDA input in this, and we
16 used it in combination. We did not want all 19 drugs on
17 the list, but we looked for high frequency of use. I
18 think we went for the more potent than the less potent.

19 DR. MATHIS: It was, actually, one of the drugs
20 we did look at, and just because we had to limit the
21 number of drugs that we considered for the final list, it
22 didn't make the cut. However, it is certainly something

1 that we can consider in light of the discussion today.

2 DR. WARD: If a study were designed of one of
3 these three, could the Hydrocortisone acetate, as
4 proposed, be the comparator, or would you want a placebo?

5 DR. MATHIS: Never say never, right? I mean,
6 you could even have more than just two arms if you did
7 need the placebo, and I think that that would be
8 something that we would need to take back.

9 Also, it would be something that we would need
10 to talk with NIH about because, of course, they are the
11 ones that have to issue the contracts, but we can
12 certainly consider that.

13 DR. LASKY: My inkling is that, because we are
14 looking for long-term effects and very subtle effects,
15 this would need large numbers and long periods of time.
16 My personal prejudice is it would have to be an
17 observational study or something closer in between,
18 because people are not going to sit within the structure
19 of a randomized clinical trial unless there are many,
20 many options and secondary treatments, which will result
21 in a multiple-sell kind of design anyway.

22 So my feeling all along is that this is going

1 to produce information about a number of topicals at
2 once, but it is something we have to deal with.

3 DR. WARD: Let me ask one other question. What
4 is your feeling about the three? Do you agree with Dr.
5 Epps that the Hydrocortisone valerate would be the most
6 important of those three that are on the list? I
7 understand the acetate, but of the these three?

8 DR. NIKHAR: Yes, I agree, I think, with the
9 ointment we do need more information out there. I agree
10 with that.

11 DR. WARD: Our obligation is to provide
12 guidance for practicing pediatricians. They have to go
13 through, frequently, the pediatricians and family
14 practitioners before they go to you.

15 Bill.

16 DR. RODRIQUEZ: I just want us to remember that
17 there are drugs where, after exposure for as little as
18 four to eight weeks, you see differences in the growth
19 and you see differences in the weight of the kids that
20 were exposed to those drugs. There were systemics, but
21 some of these things have been absorbed.

22 So therefore, what I'm trying to say is that

1 the effect on growth may actually be noticeable for a
2 segment of the population after a relatively short
3 period. Short means if you took it over a lifetime, you
4 are talking about one year, for example, et cetera, if
5 you are actually concentrating on looking at those things
6 with the appropriate monitor and all those things that
7 need to be done that most people don't use in their
8 practice.

9 DR. WARD: Dr. Mathis, let me ask you about
10 this issue of the Hydrocortisone acetate as comparator or
11 as one needing study, because it is over the counter and
12 quite old. How can we handle that, again to serve
13 pediatrics?

14 DR. MATHIS: Well, I think there are several
15 different ways that we can handle it. It is, of course,
16 off-patent, so it is difficult for us to ask the sponsor
17 for studies, although we could do that.

18 The other thing is to consider using it as a
19 comparator arm. I do agree very strongly with Dr. Nikhar
20 that here is the drug that we are holding up as the gold
21 standard for being safe, and yet we have no current data
22 on it. The data that we have, of course, are testings

1 that we would never use today to assess the safety of the
2 drug, and they are not very relevant as their means of
3 cortisol levels. We know cortisol levels have meaning
4 for an individual patient, but it is difficult to draw
5 conclusions on mean levels across a whole group.

6 We will take this back and consider it, and
7 there is a potential that you may see this for evaluation
8 next year.

9 DR. WARD: Dr. Zito, then Dr. Grogg.

10 DR. ZITO: There have been some really good
11 suggestions raised in the last few minutes, and I just
12 wanted to endorse that all three drugs, obviously, could
13 be studied as different arms in a very large study.

14 Now, obviously, you can't do that very
15 expensive testing in thousands, but you could do them in
16 subsets. You could do fancy stuff in subsets which would
17 not be as costly. That is one thing.

18 The second thing is a focus on chronic use.
19 That is, looking at the prior history or the prior use of
20 steroids would help you to define children who are at
21 much greater risk.

22 Going across all the age groups makes a lot of

1 sense because then, as you get into those adolescents,
2 you may have kids with eight, 10, 12 years prior
3 experience using steroids.

4 I was also very interested in the issue around
5 flaring, around the fact that the use sometimes is
6 encouraged by the fact that it appears to some
7 individuals they can't stop using some of these external
8 products, and how you deal with that in protocols.

9 Then, finally, to think about design issues. I
10 know it is very hard for us to change and to go forward
11 in the way that we think about what is, quote, unquote,
12 "robust" or "highly internally valid" studies, but we are
13 in a different place than we were 40 or 50 years ago in
14 terms of having very large, organized, clinical practice
15 treatment settings. I think of Kaiser as an example.
16 All their docs are well trained to use the computer and
17 to enter information, for example.

18 So if you were writing a contract that would
19 encourage responses from quasi experimental design
20 issues, it would encourage people to think that way.

21 DR. GROGG: In this world of bad news, it is
22 some good news. I think we are seeing some steroid-

1 spearing because of the immunomodulators protopic. Maybe
2 some of the studies might be concerning diaper rashes and
3 the use of short-term steroids followed by Elidel or
4 protopics.

5 DR. NIKHAR: Well, topical immunosuppressants
6 have their own problems, but we won't go down that road.

7 DR. LASKY: They aren't approved below two,
8 first of all.

9 PARTICIPANT: They are on-patent drugs, so we
10 can't talk about them.

11 DR. NIKHAR: Those drugs, yes, two years and
12 up, and they have their own issues, but we won't go down
13 that road.

14 DR. MATHIS: I think, to quote Dr. Epps, better
15 the devil you know than the devil you don't. I think she
16 said that years ago during an advisory committee
17 discussing some of these.

18 You're right, we are seeing some steroid-
19 spearing, but there is a reason why those drugs are
20 labeled as second-line and none of them for patients
21 under the age of two.

22 DR. LASKY: I think last year at the hearings

1 people mentioned ad hoc compounding of immunomodulators
2 with the corticosteroids.

3 DR. WARD: Dr. Sachs, then Dr. Woods.

4 DR. SACHS: I just wanted to make sure as you
5 thought about this that, and correct me if I'm wrong,
6 either Lisa or Bindi, but two of the drugs, the Desonide,
7 I guess, it says, "Safety and effectiveness are not
8 established in children at all," whereas the Aclovate
9 coverage says under one, as you prioritize the three.

10 DR. NIKHAR: Right. There is no as such
11 pediatric safety information for Desonide yet.

12 DR. WARD: Dr. Woods.

13 DR. WOODS: I'm generally not worried about
14 topical or inhaled steroids being overly
15 immunosuppressive in terms of risk for infection, but I
16 guess in terms of the use in young children, one question
17 that at least might be explored is, if you are absorbing
18 enough to alter your growth, could you be absorbing
19 enough to at least maybe down your response to vaccines.

20 DR. WARD: Good point. One of our difficulties
21 is, if there were 19 products that came, the sieving of
22 that to get down to sort of a precious few to go on this

1 list maybe missed some of the focus needed. I think
2 there may be a way to handle that, as you pointed out.

3 Of those three, I think, again, in a practical
4 sense, we are not going to be able to study under BPCA
5 all three of these products. There simply won't be
6 enough funds to support that. So I think we should make
7 some effort at evaluating what we think is the greatest
8 priority.

9 DR. NIKHAR: I would also like to point out
10 that the age group for the HPA axis suppression test, we
11 have encouraged going down to as low as three months, and
12 there are different cohorts of children. So children as
13 young as three months are being studied.

14 DR. WARD: All neonatologists are familiar with
15 how unreliable serum cortisol levels are in the neonate.

16 Good. Thank you very much.

17 Wayne?

18 DR. SNODGRASS: One small question, Dr. Winer.
19 Is there any data that any steroids have different
20 potencies for bone accrual or linear growth versus, say,
21 vasoconstriction or inflammatory actions?

22 DR. WINER: Well, we understand what the

1 different potencies are. Endocrinologists look at
2 glucocorticoids in terms of their action and their
3 ability to suppress, so you have the Hydrocortisone and
4 the Prednisone group, Prednisone being about four times
5 the potency of Hydrocortisone, and intermediate acting
6 would be the Triamcinolone, and then the very long
7 acting, more potent would be the Dexamethasone and the
8 Betamethasone.

9 We know the longest acting causes adrenal
10 suppression for sure, and Cushing syndrome. There is a
11 lot of data on that. Along with Cushing syndrome comes
12 osteoporosis, poor bone accrual, and lack of growth.

13 The gray area is the shorter acting, the
14 Hydrocortisone for children or adults who use that on a
15 chronic basis. I think that is really the question that
16 one should ask right now. What happens with a shorter
17 acting, even the over-the-counter Hydrocortisone, really
18 used very liberally, frequently, on a chronic basis.
19 What happens to those people. I think that should be the
20 question.

21 DR. NIKHAR: Can I also point out that although
22 the potency determines how effective a drug is and side

1 effects are directly related, it is not always the case,
2 because it depends what is in the vehicle. For example,
3 propylene glycol, which can be an additive in some of
4 these vehicles, that increases the absorption of the
5 active chemical moiety and therefore side effects.

6 DR. WARD: Let's take a break, and then we will
7 come back.

8 [Break.]

9 DR. WARD: There has been a request from the
10 FDA to go ahead and move up a couple of the drugs,
11 Sevelamer and Zonisamide, in anticipation of the arrival
12 of some of the FDA reviewers for some of the others.

13 **Review 2: On-Patent Drugs**

14 **Review of Sevelamer**

15 **Dr. Robert M. Ward**

16 DR. WARD: Let me talk -- it is actually going
17 to be quite brief -- about Sevelamer. There were only
18 two references included, and one of those was a textbook
19 about renal failure.

20 Sevelamer is a phosphate binding agent. It is
21 a polyamine, and it is available in 400- and 800-
22 milligram tablets. Its importance is that it does not

1 contain any aluminum, so that it frees us from the
2 aluminum toxicity that accompanies virtually all of the
3 other phosphate binding agents.

4 The other aspect of it is that it is a lipid
5 binder and will reduce LDL in cholesterol, sort of as,
6 hopefully, a benefit.

7 The average dose in adults is 14 grams a day.
8 So if a child is old enough to swallow tablets, they are
9 potentially treatable with this because of the lower
10 dosage forms of 400-milligram tablets. It has been shown
11 to be effective at lowering phosphate to normalize the
12 calcium phosphate product.

13 What has been interesting is, when you look at
14 the literature, the effects on parathyroid hormone, the
15 secondary hyperparathyroid hormone that accompanies renal
16 failure and phosphate retention, does not seem
17 particularly to be corrected by this, yet it improves the
18 periostitis and the other bone findings.

19 A written request was made to the company to
20 study this drug in six- to 18-year-olds, and they turned
21 it down. My understanding at this point -- somebody from
22 the FDA can correct me -- is that this is actually the

1 only phosphate binder free of the accompanying aluminum,
2 I think. Is that true? Okay.

3 So that is its importance, I think, in
4 pediatrics. These children are not dying from
5 hyperphosphatemia, but they certainly have chronic
6 morbidity and symptoms from it and their growth velocity
7 will be slowed. They simply need treatment, and it will
8 be either with this or with something else.

9 Dr. Zaoutis?

10 **Secondary Review of Sevelamer**

11 **Dr. Theoklis E. Zaoutis**

12 DR. ZAOUTIS: Not a whole lot more to add. I
13 sort of agreed that in terms of assessing the worksheet
14 or the score for it, it is a problem in these children.
15 It has chronic morbidity and may lead to visits and
16 repeat follow-ups, so in those areas I thought it would
17 be important to give it a priority score. There is no
18 data on any of the other parameters, efficacy, safety,
19 and PK/PD.

20 I thought it would be important to consider
21 studying this drug further, and I thought the letter by
22 the FDA was appropriate. I gave it a priority score of

1 eight.

2 DR. WARD: I gave it a priority score of seven.

3 I really think this is one of those very difficult
4 issues in therapeutics that everybody around the table
5 probably realizes. Widespread but low toxicity or low
6 morbidity disease or an infrequent but high
7 morbidity/mortality disease. How do you make that
8 tradeoff.

9 I think in pediatric therapeutics we have to
10 make that tradeoff and we do need to serve children's
11 interests the best way we think we can.

12 Any other comments?

13 Dr. Grylack was here. I don't know if he wants
14 to, or Dr. Temeck from the FDA?

15 **FDA Review of Sevelamer**

16 **Dr. Lisa L. Mathis (for Dr. Laurence Grylack)**

17 DR. MATHIS: Actually, Dr. Grylack gave me his
18 comments, and we discussed this. We really don't have
19 anything in addition to add.

20 **Open Discussion**

21 DR. WARD: Yes, Jeff.

22 DR. BLUMER: A question. It would seem that

1 with something like this, and considering that it is an
2 on-patent drug, the formulation isn't going to work. I
3 mean, this is just sort of a point of information. I'm
4 just curious.

5 DR. MATHIS: For the on-patent drugs, as well
6 as, actually, for the off-patent -- but it is a little
7 bit easier with an on-patent because there is a
8 pharmaceutical company that has that infrastructure -- we
9 can require that they make an age-appropriate
10 formulation. If they are able to demonstrate from a
11 chemistry standpoint that they cannot make an age-
12 appropriate formulation, we can ask them to give us a
13 compounding recipe that we can include in labeling. We
14 have been able to do that in the past.

15 As far as the off-patents go, we can still
16 require that, and we ask that, but maybe Dr. Mattison can
17 address this a little bit more. It is more difficult as
18 we are asking private investigators to study these drugs
19 to have them also have the chemistry infrastructure to
20 come up with new formulations.

21 DR. MATTISON: I know that you all are
22 frustrated by the lack of pediatric formulations. There

1 are several different approaches that we can take. One
2 is through our SBIR activities. We can try to stimulate
3 that.

4 So we are working to try to develop
5 formulations for off-patent drugs that are still used
6 fairly extensively that make sense in terms of pediatric
7 dosing.

8 You are looking in the right direction. That
9 guy back there with the red tie is one that has been
10 stimulating our discussion in that direction, Jeff.

11 DR. ZITO: Let me ask a question around that
12 issue. To what extent do you promulgate information
13 about the need for it to departments that would cut
14 across chemistry, pharmacy, et cetera?

15 DR. MATTISON: Are you asking me? We have done
16 it to some extent. We need to do it more.

17 DR. ZITO: The website, for example. It would
18 be so nice to see one-pager that says there is a great
19 need.

20 DR. WARD: As Dr. Mattison pointed out, this
21 one is of those special situations where this is still
22 on-patent, and with hyperphosphatemia with renal failure

1 in infancy, they are certainly not going to be swallowing
2 400-milligram tablets. So we can, I think, express
3 ourselves that a formulation is needed because renal
4 failure will start shortly after birth in some of our
5 kids, unfortunately.

6 Alan.

7 DR. STILES: So, what is the question to this
8 group about this drug?

9 DR. WARD: The question is, is this a priority
10 for study in pediatrics. If it is and a formulation is
11 needed, I would ask you to go ahead and write in to the
12 side "liquid formulation is needed." That request can be
13 made by the agency to the sponsor, even though the
14 sponsor has turned down studying this drug under the
15 request as issued to them.

16 Rosemary, do you want to comment about this? I
17 think I'm correct, but have I made a mistake?

18 DR. MATHIS: Our office director, Rosemary
19 Roberts, is here, and so I was just deferring to her to
20 see if she had any additional points to make about
21 formulations or if we have made them all.

22 DR. ROBERTS: I would just say that we share

1 with you the frustration over the formulation issue.
2 Ideally, we would like to see commercially available
3 pediatric formulations for all the products that are used
4 in the pediatric population.

5 That said, it is not a commercially viable
6 option for many companies to take and put in the work.
7 Sometimes these are extremely difficult formulations to
8 make in a liquid preparation. Taste is always a problem.

9 Then, once they do make it, if they put it on the
10 market, then they have to maintain that line and undergo
11 all the CMC that is necessary.

12 So recognizing that, we have indicated and we
13 have seen, especially in the area of some of the
14 antihypertensives that have had studies since the FEDAMA
15 and the BPCA were passed, pharmacy compounding recipes
16 that we are putting directly into the labeling.

17 I think prior to FEDAMA and the BPCA, the
18 agency was really negative on the thought of putting
19 anything other than a commercially available formulation
20 in-house supply, but we recognize that as long as these
21 are done appropriately and we get some stability
22 information on how to store it and how long it will be

1 stable, that this is much better than having nothing for
2 these children.

3 Unfortunately, we have seen studies done and
4 then, in the end, there is no appropriate formulation
5 available for children. So that is certainly a down side
6 to that.

7 So anything that you would suggest that could
8 be helpful to encouraging industry to do formulations for
9 children, we certainly would appreciate. I think the
10 suggestion to put up on the website that a formulation
11 for this particular product would really be advantageous
12 for our children would be a good thing to do.

13 DR. WARD: In another life -- we live many
14 lives -- as Committee on Drugs chair, we tried to use
15 that sort of bully pulpit to pressure some companies into
16 providing formulations that we felt were very important
17 for children. I think we can continue that effort.
18 Maybe it will be extemporaneous, but at least we can
19 encourage them to make the effort.

20 DR. SNODGRASS: Is this an orphan drug
21 relatable to a small enough population or not? Just for
22 the particular age group?

1 DR. MATHIS: I actually don't know if this has
2 orphan drug designation, although the fact that it is
3 getting a written request doesn't necessarily preclude
4 that. If we were requiring them to do these studies
5 under PRIA, we would know that it wasn't an orphan.

6 I don't know what the status of it is, although
7 I don't remember reading that it was orphan. That goes
8 unknown to us sometimes, unless we actively ask.

9 DR. WARD: I don't know the frequency of
10 chronic renal failure in pediatrics, particularly young
11 infants below the age of two.

12 DR. CLARK: I'm Mary Beth Clark from GenSci. I
13 want to just make a very brief statement.

14 No, it is not an orphan indication that we
15 filed for at all. Just to give a very brief update, I
16 think your thoughts on the liquid formulation are very
17 important, and you should make note of that. There are
18 certain things that I can't discuss here in an open
19 forum, but there are things that we are looking at.

20 We did receive a written request from FDA on a
21 protocol that we sent them. They had wanted an extended
22 safety follow-up that, based on problems we saw in

1 earlier studies, we didn't think that we could meet the
2 timeline that we were given by FDA. We went ahead with
3 our study as designed, which didn't meet the written
4 request.

5 We have just completed the study. We are
6 submitting it to FDA. We are in discussion with FDA
7 about future studies as well, just so that you know that.

8 DR. WARD: Thank you. Appreciate having the
9 sponsor here to hear our comments.

10 Let's move to Zonisamide for epilepsy. I
11 believe it is Dr. Woods.

12 **Review of Zonisamide**

13 **Dr. Charles R. Woods**

14 [PowerPoint presentation.]

15 DR. WOODS: This is a drug I have had to learn
16 about, at least in a capacity as a general inpatient
17 attending. At times we admit children for our neurology
18 service with various types of seizures, so this is an
19 antiepilepsy drug.

20 It is classified as a sulfonamide. It is
21 unrelated to other drugs in the class, and this just
22 gives you the basic structure. It is supplied in capsule

1 form only.

2 It has been available in Japan and South Korea
3 since 1989. That is where almost all of our pediatric
4 data comes from. They have a lot of experience with it.

5 It appears well tolerated in reports. It is effective
6 against a broad range of seizures, or a broad spectrum
7 anti-convulsant agent.

8 There have been 14 studies amongst Japanese
9 children, although basically all of them have been open-
10 label, with only one in which there was a small
11 randomized component.

12 No RCTs in children in the U.S. or Europe.
13 Again, it has fairly broad potential and may be even most
14 important in some of the much more difficult seizures
15 types we see in children, infantile spasms and linitis
16 gastric syndrome.

17 The precise mechanism of action is not
18 completely clear. It appears to block both sodium and
19 calcium channels. It may stabilize membranes. It does
20 bind to some GABA benzodiazepine receptor complexes, but
21 it doesn't appear to potentiate GABA synaptic activity.
22 It has some weak dopaminergic and serotonergic

1 neurotransmission effects. It also has a weak carbonic
2 anhydrase enzyme inhibition activity, which may be
3 important in some side effects that I will review in a
4 minute.

5 There are some animal models suggesting it may
6 have some neural protection against hypoxemia, although
7 it is not completely clear that would translate into
8 infants or children.

9 Interestingly, it does not inhibit or induce
10 the P450 cytochrome system, which is a nice feature of
11 the drug. It is both acetylated and reduced. I will
12 show you a little more on that in a second. Certainly,
13 liver disease can reduce its clearance.

14 Drugs that induce liver enzymes can increase
15 its clearance, also, so while it doesn't necessarily
16 impact other drugs, other drugs can impact it.

17 Half-life is low, like many of the
18 anticonvulsants, 50 to 70 hours. It could be shorter in
19 children, and maybe shorter dose intervals are required,
20 but we really need more information on that topic. The
21 Japanese data suggests younger children may need higher
22 doses, and the dosing, maybe, should be based on surface

1 area rather than weight.

2 This may be more in the pharmacogenomic arena,
3 but at least in terms of the acetylation, there are
4 differences in frequencies of poor acetylators in
5 different populations. So it may be that if you
6 acetylate rapidly and you clear it better, you might have
7 less acetylate build-up of toxic levels. So it may be
8 safer in Japanese children and Chinese children than it
9 would be in other groups. This would be something that
10 needs to be studied. Although it is not completely clear
11 if you acetylate poorly, you may still clear it just fine
12 from the reduction aspect, but again, this is something
13 that needs further study and in different populations.

14 Adult data from the package insert. I think
15 probably most of this is based on the U.S. showing
16 reasonable both reduction in partial seizures and
17 response. Response generally is taken as a 50 percent or
18 more reduction in numbers of seizures in a specific time
19 period in epilepsy studies.

20 As usual, read the instructions very, very,
21 very carefully.

22 [Laughter.]

1 DR. WOODS: Adverse effects. These are the
2 adult data, again. Compared to placebo, some slight
3 increases in a number of issues, anorexia being one that
4 may be of importance and may be relevant to growth or
5 weight gain in children.

6 Dizziness and ataxia seen somewhat more than in
7 placebo recipients. Also, in adults, a little bit of
8 tendency towards some confusion. Maybe some difficulty
9 concentrating. Who knows if it would work for ADHD in
10 some other way.

11 Can see depression and occasionally even
12 psychosis, but these seem to be fairly rare events
13 overall. Fatigue being another side effect seen in
14 adults.

15 A couple of things to note about this, at least
16 in adults. There seems to be some predisposition toward
17 kidney stone formation. Not quite sure if this is a
18 sodium channel, a calcium channel, carbonic anhydrase
19 inhibition issue. It does seem to occur, at least in the
20 things I read on this, in people who might be predisposed
21 to have stones anyway. I'm not sure that this would be
22 as big an issue in children as it would be in adults, but

1 again, it would be something that would need to be looked
2 at.

3 Its current indications in the U.S. are for
4 treatment of partial seizures in adults with epilepsy.
5 It probably, again, has a much broader spectrum than
6 that, and probably is being used in children, and is
7 being used in children, off-label in this country,
8 especially for refractory seizures. We really don't have
9 much data, or no data, in Europe and the United States in
10 kids under 16.

11 My wife found this on a greeting card years
12 ago, and it applies to most of my life, I think.

13 [Laughter.]

14 DR. WOODS: Amongst Japanese children, we do
15 have some pharmacokinetic data. This study shows
16 basically you get higher levels in older kids, and then
17 it shows, I guess, on the top quarter that there is
18 really no impact of using Zonisamide on Carbamazepine,
19 but there can be an impact of Carbamazepine on
20 Zonisamide.

21 You probably can't read this very well, but the
22 next few slides are summaries of the Japanese studies in

1 children, five studies looking at Zonisamide as
2 monotherapy for partial generalized seizures. Amongst
3 those with partial, they saw some impact in about 78
4 percent, and in those with generalized, about 71 percent.

5 Fairly large numbers compared to a lot of things we have
6 in kids. These are not randomized. These are open-label
7 data.

8 If you look at Zonisamide as adjunctive or
9 mixed therapy -- meaning, I guess, mixed where they had
10 some kids open-label, some randomized, but primarily
11 adjunctive therapy here -- a little bit less response, 34
12 percent, 15, and then, when it was mixed, slightly better
13 numbers. Probably a lot of these kids are having it
14 added as an adjunctive therapy because they have more
15 refractory seizures in the first place, so that may be
16 why their response rates are a bit lower there.

17 Then, in children with infantile spasms, there
18 were five studies that looked at this. Twenty-two to 36
19 percent response rates, which is pretty good for that
20 disorder. You will take just about anything. ACTH is
21 the primary therapy there. It has lots of side effects
22 and is difficult to administer, so if this were to be of

1 benefit in that group of children, it would be a good
2 addition.

3 One study in the U.S. on this showed a 33
4 percent impact on infantile spasms. So again, within
5 that range. Again, these are observational studies.

6 Then, on the kind of wastebasket linitis
7 gastric syndrome, which is also very refractory, response
8 rates in the range of 26 to 50 percent, which if that
9 were to hold up, would be a nice benefit. Even if that
10 is just reduction and not elimination, that would be
11 important for those children and their families.

12 Progressive Myoclonus epilepsies, which I
13 really don't know much about except apparently they
14 progress and they are severe and they don't respond well
15 to much of anything, there may be some effectiveness of
16 Zonisamide in some of these disorders. Again, this is a
17 heterogeneous group. Some may respond, some may not, but
18 again, anything that helps, even for a year or two, is a
19 useful part of our inventory.

20 Adverse effects in pediatric studies. Again,
21 not huge numbers in these trials to pick up severe rare
22 events. You can't read this very well, but some of the

1 ones, 13 to 18 percent, maybe even up to 34 percent in
2 some of the trials, anorexia being in there. Rashes do
3 occur, and maybe salivation issues in a few. Not that
4 different from the adult data.

5 This was the one sort of randomized trial or
6 part of a trial in Japan that actually systematically
7 collected side effect or adverse event data, showing
8 similar numbers of about 23 percent somnolence, 15
9 percent or so ataxia, some cognitive impairments in a
10 few. That may be more severe in children who already
11 have underlying cognitive issues. Irritability also seen
12 in there.

13 Then there is something called oligohidrosis,
14 and this may be due to the carbonic anhydrous inhibition
15 activity that reduces sweating. This is apparently a
16 fairly common side effect, although it is probably not
17 clinically significant most of the time. There are a
18 couple of reports in the literature, I think, in 18-year-
19 olds and maybe adults with heat stroke perhaps
20 attributable to this. It will be something that will
21 need to be looked at.

22 So in summary, at least in the Japanese

1 experience, they feel that it is well tolerated under
2 gradual titration to target dose. That is considered to
3 be about 8 milligrams per kilo per day. Adverse effects
4 seem generally mild or in line with a lot of the other
5 anticonvulsants. That is not to say there aren't adverse
6 effects with this.

7 I guess there would be two ways to look at
8 this, ultimately, as monotherapy or, I guess, new
9 epilepsy issues. Would we look at that first, or with
10 that more as an adjunctive agent for refractory seizures.

11 So certainly, in the latter case, some of these side
12 effects may be more tolerable than they might in the
13 former.

14 Frequency of adverse events. Interestingly,
15 many of these children were on other medications, so it
16 is lower for Zonisamide alone. When you have one other
17 AED, 37 percent; two or more, up in the 40 to 50 percent
18 range. I don't know that this speaks to drug
19 interaction, but maybe the action of the side effects
20 that were caused by the other agents.

21 In the studies in Japan, about 12.5 percent
22 discontinued for either adverse event or the combination

1 of drugs they were on either wasn't working or they were
2 having side effects.

3 Target serum concentration, at least so far,
4 would seem to be 10 to 40 micrograms per mL, start at 1
5 to 2 kilo per day and work up over several weeks to that
6 8 milligram per kilo per day dose.

7 Since we are having flu problems, I thought you
8 might like that. "The company is giving free flu shots,
9 Wally. The shots will be delivered by wealthy
10 stockholders who will hunt you down and shoot you with
11 flu darts." Wally is initially optimistic, thinking,
12 "Well, at least I won't get the flu."

13 [Laughter.]

14 DR. WOODS: We could probably manufacture this
15 kind of flu shot more quickly.

16 [Laughter.]

17 DR. WOODS: I hope you feel this way.

18 "I just had a good meeting." Dogbert says,
19 "Well, maybe it just didn't last long enough to reveal
20 the incompetence of the attendees," which is me in this
21 case.

22 I think we are having a good meeting so far.

1 [Laughter.]

2 DR. WARD: So we will keep on pace.

3 DR. WOODS: I guess, to answer the questions,
4 we need more information on pharmacokinetics. We need
5 more information on efficacy, more information on safety.
6 This is not necessarily a leading cause of mortality,
7 the seizures, but a fairly leading cause of morbidity in
8 pediatric patients.

9 There is a fair amount of hospitalization for
10 seizures in general, maybe smaller for the more
11 refractory ones and maybe less than we are used to
12 seeing, but I think I would still give it a one there.

13 Not necessarily lengthy hospitalizations very
14 often, although that might not be true for infantile
15 spasms early on, depending how we define "lengthy."

16 Frequency of physician visits. It keeps our
17 pediatric neurologists and neurologists in general very
18 busy, so a lot of pediatric seizures. It does account
19 for a fair proportion of our total pediatric
20 hospitalizations.

21 DR. WARD: I blinked. The formulation, liquid
22 formulation?

1 DR. WOODS: We need a liquid formulation, also.
2 It is only in 25-, 50-, and 100-milligram tabs right
3 now. Probably, you could look at issues of metabolism in
4 different racial/ethnic groups. It may not be a big
5 issue but it needs to be explored. There are
6 alternatives, but I would give it a one there still,
7 because for some of the kids with refractory conditions
8 we need more agents in those.

9 So I come up with a score of 10 in my look at
10 this for epilepsy in general.

11 DR. WARD: Dr. Zito?

12 **Secondary Review of Zonisamide**

13 **Dr. Julie Magno Zito**

14 DR. ZITO: I will talk while Glen is loading in
15 the numbers so I can show you the utilization data for
16 this drug from a Medicaid population.

17 I'm not as enthused as Dr. Woods. I know that
18 there is a great need for more information on every new
19 drug, or relatively new drug, but this, for my priority
20 list, would go pretty low.

21 I do have a little bit of experience learning
22 how to monitor antiepileptic drugs. When I was at the

1 University of Minnesota, I worked for about a year and a
2 half with Ilan Lepic [ph], who is an expert in the field.

3 I learned a lot about the complexity of managing seizure
4 disorder, including the over-use of meds, which then
5 becomes a new problem in itself.

6 So the whole field focus on adjunctive
7 treatments becomes a really difficult issue, and this is
8 only approved for adjunctive use. So already your
9 enthusiasm should be a little bit different than if it
10 were, say, for mild therapy.

11 I want to go back to the point that Ilan is
12 interested in, I guess. They have written a letter to
13 the FDA saying, so I guess there is a six-month marketing
14 exclusivity there, or related to that. Why would they be
15 writing you a letter?

16 DR. LASKY: Unless you have something else, I
17 think it is the other way around. FDA has written a
18 letter to them, and they turned it down.

19 DR. ZITO: So their response, I thought, was
20 positive, was it not?

21 DR. LASKY: Is there a response?

22 DR. ZITO: The way I read the letter and my

1 interpretation is that they would be interested in
2 conducting efficacy and safety studies. So that tells me
3 something. There is interest in marketing, and there is
4 a market need there.

5 The second point relates to efficacy. I think
6 the data are incredibly weak for adjunctive use, 20
7 percent, 25 percent responders. Even in psych studies we
8 do better than that. So I thought the numbers were not
9 persuasive in regard to its role as adjunctive.

10 The third point I would like to make, also,
11 then around in vitro efficacy, there also wasn't such
12 good stuff.

13 The fourth point I would like to make, and it
14 relates, really, to my main issue of why I am not
15 enthused, relates to safety. The Japanese issue is
16 really important because American physicians prescribe
17 drugs much more intensively, at much higher doses almost
18 than the rest of the world. So you need to immediately
19 think that people who don't see a response are going to
20 push the dose.

21 Already, we have now a good indication of the
22 clinical pharmacology that is very suggestive that

1 oligohidrosis and fever, while maybe hasn't killed
2 anybody yet, is a potentially serious thing where there
3 isn't good, close clinical monitoring to recognize that
4 that fever is actually related to meds rather than to
5 just cough and cold or flu.

6 So the carbonic anhydrous inhibition, which we
7 have had those drugs for many, many years. They are not
8 world leaders in the world of epilepsy.

9 Then, of course, there are the skin rash issues
10 with a number of these drugs that have come out as
11 adjunctive therapy in recent years. We worry a lot about
12 Steven Johnson syndrome and toxic necrosis syndrome. So
13 there is a potential there.

14 Then, the final point I will make is that the
15 anticonvulsants are now no longer for the treatment of
16 seizures. We have, wow, mood stabilization for
17 aggression conduct disorder in children, but aggression
18 in adults and failure to get mental health drugs to fully
19 control people.

20 So you should expect that there will be some
21 experimentation for the purpose of mood stabilizer
22 certainly at least in the teenage population, and then

1 that would mean that you could be looking at kids on
2 regimens that include stimulants and perhaps even an
3 antidepressant and this drug for that purpose. That will
4 have nothing to do with the use in seizures.

5 So having said all that, now I will show you
6 that nobody is using it in the data set that I had. But
7 then, new drugs don't get used. They get adopted slowly,
8 so it is not surprising.

9 DR. WARD: If the data actually show
10 essentially no usage, we are probably okay without seeing
11 it.

12 DR. ZITO: I mean, it is stark, so stark we
13 couldn't provide a prevalence. The numbers were too
14 small. We had, actually, 10 less-than-18-year-olds in
15 the year 2000. Now, I'm sure that through '01, '02, '03,
16 each year we have grown by another 30 kids, something
17 like that.

18 DR. WARD: Your denominator for that 10 or 30
19 kids in that database is roughly?

20 DR. ZITO: That is what I could show you. I
21 haven't memorized it.

22 DR. WARD: If it is that low, that is okay.

1 DR. LASKY: It is the entire Maryland Medicaid
2 population, which is one-third of the children pretty
3 much in Maryland.

4 DR. ZITO: Oh, you wanted to know the total
5 denominator of enrollees?

6 DR. WARD: Yes.

7 DR. ZITO: It is 301,000.

8 DR. WARD: So we are talking 10 or 20 or 30
9 over 300,000. That is a small number.

10 DR. ZITO: I was reaching for the number of
11 anticonvulsant users. It is 10 out of 20,000 or
12 something like that.

13 **FDA Review of Zonisamide**

14 **Dr. Lisa L. Mathis**

15 DR. MATHIS: Just from the FDA perspective, one
16 of the reasons why this ended up being referred to the
17 foundation is just people feeling like there is a small
18 population of very desperate patients that need
19 alternative therapy. So I think nothing in addition to
20 what has already been shared by the experts, but just to
21 consider that these are patients that don't always have
22 something else.

Open Discussion

DR. MEYTHALER: I just have a couple of questions on that. There are a number of other drugs that have been used in pediatric seizure control off-label. Ten have come out in the last six years, like Topiramate and Lamictal, some of which have first-line indications as well as second-line or adjunctive indications.

I'm surprised that these weren't recommended, unless the companies are proposing them right now, because those tend to be used second-line. I helped write some of the guidelines for seizure prophylaxis in head injuries. So that was one of my issues with it.

The second issue, though, is, I will tell you there is a real secret use of this drug off-label for weight and obesity, both in kids, adults, et cetera. This drug is being used heavily in weight control because it does drop it. You brought that up, but this is under the guidelines that there are a lot of people using it.

One of the docs in my clinic used up our whole supply of this drug that we had as samples, and it was all in weight reduction, not in seizure control, and we

1 had a lot of seizure patients.

2 DR. GROGG: For his patients or himself?

3 [Laughter.]

4 DR. MEYTHALER: So that is another issue. It
5 is being used off-label. In fact, a lot of people feel
6 Zonisamide may be selling almost 50 percent of the drug
7 now for that. It is not being used as much for anti-
8 seizures, and that is why I think the drug company turned
9 it down.

10 DR. WARD: Charles.

11 DR. WOODS: Let me just comment, my enthusiasm
12 for this drug is more that we should study it because I
13 think we do have a need in kids for at least adjunctive
14 measures.

15 I do share Dr. Zito's concerns about some of
16 the side effects, and certainly, they may be more severe
17 in some populations than others.

18 DR. MEYTHALER: The side effect profile,
19 though, is very when you compare it to Tegretol,
20 Depakote, or even Dilantin.

21 DR. WOODS: That is why, also, I am not as
22 worried about that, because these other medications are

1 toxic and this may not be much more severe. The other
2 thing that gives me a little encouragement, even if it is
3 not highly efficacious, is that it doesn't have much
4 interaction with the other agents. So those are things
5 that, to me, say I would study it, but I don't know that
6 it is going to be useful.

7 DR. ZITO: I think the safety profile deserves
8 a delay in conclusions. It is a thirteen-fold difference
9 between the occurrence of oligohidrosis and fever in U.S.
10 kids than in Japanese kids, so they didn't have it over
11 there. They didn't experience that problem.

12 My thought is that unless you do something to
13 really know that you can control this by appropriate
14 dosing, I think it is going to happen again in United
15 States children. In western Europe, the same thing
16 happened.

17 DR. WARD: We just study it in Minnesota.

18 DR. SNODGRASS: Just from a general point of
19 view, I think that there is this subgroup of patients.
20 The benefit-risk ratio considerations of a drug like this
21 are in favor of certainly studying it. I mean, yes, you
22 look at the side effect profile, you certainly would, but

1 there is a group of patients out there that clearly need
2 anything else you can bring to bear on that therapy.

3 DR. WARD: Dr. Zito, I was impressed with this
4 issue about adjunctive treatment. The reason it is
5 adjunctive is because they fail the first line, so if it
6 does add something to a population that is relatively
7 desperate for seizure control and their function in
8 school or life is compromised, it may be an important
9 adjunct.

10 Your issues about safety are pivotal. Why
11 would there be a thirteen-fold difference. Is it failure
12 to look at that and recognize it and search for that in
13 the original studies? Quite possibly.

14 Charles.

15 DR. WOODS: The other thing is, average ambient
16 temperature in an area may impact that issue.

17 DR. WARD: Absolutely. I wasn't facetious
18 about studying it in Minnesota.

19 [Laughter.]

20 DR. WARD: Dr. Epps.

21 DR. EPPS: I have a question and a comment.

22 Question: Would this have any effect on those who were

1 G6PD deficient, and is that something that is done at
2 baseline?

3 DR. WOODS: That is actually in the package
4 insert already that if used that should be looked at. So
5 I think that would be addressed.

6 DR. EPPS: Secondly, since we are faced with
7 Generation O for obesity and it is a huge problem, and
8 although I don't advocate drug loss for weight loss in
9 young people, you may want to add that as an indication
10 for study for those who are really a problem.

11 DR. WARD: Bill.

12 DR. RODRIQUEZ: I also have a question about
13 the kidney stones. Those were the ones who demonstrated
14 severe enough blockage, et cetera, for pain, I assume.
15 That is the way they were actually following. The
16 question is, I wonder how much of these patients do have
17 this classification in their kidney area.

18 DR. WOODS: I didn't see any specific
19 information on that aspect, but it would be something
20 that should be looked at.

21 DR. WARD: Nephrocalcinosis.

22 DR. LAWLESS: In any of the reports, did any of

1 these kids go to surgery?

2 DR. GROGG: I think the kidney stone data
3 really are from adults.

4 DR. LAWLESS: That is where the confusion is.
5 Anybody that has a tendency to have fevers or not to
6 sweat, you go to the operating room and the first thing
7 they will start talking about is relieving hyperthermia.

8 So especially in a high-risk group like this, we are
9 going to be looking at it anyway. The idea that if all
10 of a sudden you have this group with this high prevalence
11 and you go to surgery, I will guarantee you that most
12 anesthesiologists will probably recommend that that
13 definitely has to be studied, because they will stop the
14 case.

15 DR. MEYTHALER: Is this oligohidrosis a warning
16 in the label at this point in time for adults, do you
17 know?

18 DR. MATHIS: Debi Avant says yes.

19 Is it in labeling?

20 That actually is a concern with Atropine and
21 Atropine-like drugs, because you have patients on
22 Scopolamine or Glycopyrrolate that go to Disneyland and

1 they overheat because they can't sweat.

2 It is not always Disneyland.

3 PARTICIPANT: Yes, it is.

4 DR. WARD: It is, okay.

5 Other discussion?

6 Has everybody discovered the extra sheets, the
7 yellow ones? These are for rating of these medications.

8 We will move on backwards to Griseofulvin. Dr.
9 Grogg will present, and Dr. Blumer will discuss.

10 DR. GROGG: I would suggest to you that having
11 a kidney stone could give you a seizure.

12 [Laughter.]

13 DR. GROGG: I would also suggest that you do
14 not get to massage each other again. Not during this
15 lecture at least.

16 **Review 4: Off-Patent Drugs**

17 **Review of Griseofulvin for Tinea Capitis**

18 **Dr. Stanley E. Grogg**

19 [PowerPoint presentation.]

20 DR. GROGG: Tinea Capitis. Clinically,
21 symptoms vary. We have a dermatologist here that
22 probably sees some of the resistant forms, but vary from

1 minimal pruritus with little or no hair loss -- so mine,
2 again, is not from Tinea Capitis -- severe tenderness,
3 oozing, and permanent scarring can occur. I think the
4 permanent scarring is the reason primarily for treatment.

5 Systemic treatment is required because of the
6 hair shaft and the fungus getting down into the hair
7 itself. Topical antifungal agents cannot penetrate and
8 sufficiently eradicate the infection. They may help with
9 transmission and contagiousness, but they do not help
10 with treatment.

11 Available brands. Grifulvin is in the micro-
12 size tablet of 250 and 500 milligrams, and there is a
13 125-milligram suspension. I would suggest to you to put
14 on the bottom of the list there whether you recommend
15 further study or not that it be available in the 250 for
16 5 cc concentration, because 125 requires a lot of drug
17 intake.

18 Gris-PEG is also available, which is the ultra
19 micro size, and it comes in 125 and 250. The reason it
20 is a smaller dosage is you do not have to have as much of
21 the ultra.

22 So in the micro size, the dosage is 10 to 20

1 milligrams per kilo by mouth. According to the insert,
2 two to four weeks, but that doesn't seem to work in
3 therapy any longer with a maximum of one gram a day.
4 Again, going to McDonalds before you take the medication
5 seems to help. This is not against McDonalds, it is just
6 indicating that a fatty meal helps to increase
7 absorption.

8 Comments. Because of resistance, many studies
9 recommend 20 to 25 milligrams, which is what we have been
10 using in our continuity clinics for some time, for six to
11 eight weeks of therapy rather than the original
12 recommendation of 10 to 20 for two to four weeks.

13 Tablets can be crushed, and that is a
14 reasonable mechanism of giving a higher dose in a smaller
15 amount.

16 Now, the ultra size or the ultra micro size,
17 such as Gris-PEG, the efficacy of GI absorption of the
18 ultra crystalline Griseofulvin is approximately 1.5 times
19 that of the micro size. So you get a little better
20 absorption with a smaller dosage by using the micro size,
21 and this too can be crushed and mixed with food, but it
22 is a little more expensive.

1 Contraindications and cautions.

2 Hypersensitivity to the drug class components, porphyria,
3 URIA in there. Pregnancy, caution. It is derived from
4 Penicillium mold. However, there has been no evidence of
5 any type of significant reactions if a patient is
6 allergic to Penicillin, but I would hesitate to use it if
7 you had an anaphylactic reaction to Penicillin.

8 Caution if impaired liver and renal function,
9 which is apparently more of a problem in adults than in
10 kids.

11 Possible drug interactions. I have just listed
12 a few, but some of your antiepileptic agents. It can
13 have drug interactions, increasing or decreasing dosages.

14 Contraceptives, bad situation for teenage girls. The
15 other thing, you can't drink alcohol. The drug doesn't
16 work as well.

17 Some of your other antifungal agents will
18 affect the drug concentrations, like Warfarin. Some of
19 your transplant patients may have problems in
20 hypocholesterolemia people.

21 Some of the other drugs that are used are
22 antipsychotics and even aspirin can have an effect.

1 Serious reactions are quite rare in kids but
2 include granulocytopenia or hepatotoxicity. That is the
3 recommendation in the brochure to get CBCs and liver
4 functions, but at least in my reading and my experience,
5 rarely do we get CBCs and liver functions in these kids
6 unless they are going to have to be treated for more than
7 two months.

8 Common is rashes, urticaria, nausea, headache,
9 confusion, vomiting, and all the other things that you
10 see in most of your drug interactions that can happen.

11 This is a picture of my wife just recently.
12 She had a 103 temperature and a rash, and I knew she had
13 West Nile virus. She was on Lamisil. The Infectious
14 Disease person came out to the house to make a home call
15 because I was in Washington, D.C., at the time, and told
16 me no, if we take her off the Lamisil and put her on a
17 course of Prednisone, she will feel better fast, which
18 she did. So you can get drug reactions.

19 She told me not to show that picture, by the
20 way.

21 [Laughter.]

22 DR. GROGG: Griseofulvin PK/PD information.

1 Variable absorption. Twenty-seven to 72 percent of the
2 oral dose. Increase, again, with fatty meal, and also
3 100 percent with the ultra size formulation.

4 Can be given once a day, but if you are giving
5 something for two months, once a day is bad.

6 Don't dare tell her I showed that.

7 Needs increased milligram per kilo because of
8 increasing resistance that is present, and treatment is
9 now recommended, as I said, for six to eight weeks
10 instead of the four weeks.

11 There are many studies available. Thus, I gave
12 it a high ranking. The more I read, the higher the
13 ranking.

14 It is fungistatic rather than fungicidal, like
15 Lamisil is fungicidal. It seems to interfere with
16 mitosis, inhibited by disrupting the mitotic spindle
17 structure and arresting cell division at a meta phase
18 stage -- I think you think I know what I just said, don't
19 you? -- and inhibits nucleic acid synthesis and possibly
20 antagonizes chitin synthesis in the fungal cell wall.
21 Now we know what it is.

22 The two common forms in the United States are

1 the Trichophyton, which represents the highest amount,
2 and Microsporum. We used to use the Woods lamp for
3 diagnosis. Well, that is only good for the microsporon,
4 and that is less than 20 percent, more like 10 percent of
5 the cases now.

6 The skin, a PK/PD continuation here. It is
7 excreted mainly in the sweat and, to a lesser extent, the
8 sebum. In serum levels, the big concentration is about
9 four hours, with a half-life of 24 hours. Thus, we can
10 give it once a day.

11 It is markedly reduced within 48 to 72 hours of
12 actually stopping the drug and metabolized in the liver
13 and excreted in urine and feces. Thus, if a patient
14 forgets to take it because they go with dad over the
15 weekend, it may drop to zero and then be a problem.

16 Pediatric information and efficacy, abundant
17 reviews in the literature. Used basically in Express
18 Scripts of two and a rank of five safety. Available for
19 United States. It is the only drug indicated for Tinea
20 Capitis for kids two and above, and it has been shown to
21 be very safe. You should consider CBC and liver function
22 studies.

1 I think the reason it is on the list is because
2 two and below is where we don't have an indication at the
3 present time. Most of the kids are over two years of age
4 that have Tinea Capitis, but I do see them as young as
5 six months.

6 It is associated with a high frequency of
7 physician visits for children, mostly pre-adolescents.
8 Most common infection in young urban children, crowded
9 situations again, and it is a chronic condition with
10 possible scarring if not treated, thus giving lifelong
11 implications of psychological types of interactions.

12 The instance does seem to be increasing.
13 Daycare helps with different things.

14 Increased incidence in African Americans. It
15 tends to be more prevalent in African Americans than in
16 Caucasian populations.

17 Just to give you an idea of the various costs,
18 you can see the ultra micro size is not utilized in my
19 Medicaid practice because the increased cost is not
20 covered on the formulary, but it is about \$85 or \$86 per
21 treatment course, versus \$49, and the suspension is \$43.

22 Again, because of the large volume required, I

1 would recommend that it be put on the bottom of the
2 sheet. A 250 for 5 cc suspension would be nice.

3 Alternative therapies are available. Lamisil,
4 in particular, has a shorter duration of therapy needed.

5 Four weeks with greater than 80 percent efficacy. It is
6 fungicidal in its action rather than -static, and perhaps
7 cross therapy could be utilized, where you give it for a
8 week and stop for two weeks and repeat.

9 Others that might be available but in the
10 literature didn't appear to work as well as Griseofulvin
11 in the higher concentrations were Sporonox, the Diflucan,
12 and Nizoral.

13 Griseofulvin and Terbinafine in tablet form are
14 comparable in price and the least expensive. A liquid
15 form of Fluconazole, or Diflucan, is slightly less costly
16 than Griseofulvin if given for only 20 days, so if you
17 were using it short term. Itraconazole is the most
18 expensive of the agents.

19 So, comments. The availability of an oral
20 suspension and the absence of blood test monitoring
21 support Griseofulvin's use in children, especially if it
22 was available in the 250 for 5 ccs. Presently, it is the

1 only drug indicated by the FDA for Tinea Capitis, but it
2 is only approved for greater than two years of age.

3 The comments against its further evaluation
4 would be the increasing duration of therapy and the
5 increased dosage necessary for treatment. With the
6 increased dosage, a big problem. You are talking two
7 tablespoons a day for some of these larger kids who are
8 crushing the tablet up. With the larger dosage and the
9 extended time period, we may need lab monitoring of the
10 CBC and liver function. There is no standardized
11 sensitivity test that I'm aware of that is readily
12 available.

13 So I think this is somewhat confusing, whether
14 you are a dog or a chicken walking behind the dog, as to
15 what is going on.

16 [Laughter.]

17 DR. GROGG: So even though I gave it a high
18 score, everything is high for me. I'm a very optimistic
19 person, if you can't tell. Because of the reasons in the
20 previous slides and the availability of new drugs such as
21 Lamisil, even though my wife had a reaction to it, I
22 would recommend that Griseofulvin receive low priority

1 for future listings and discussions for the reasons I
2 have mentioned.

3 That completes mine for the day. Thank you.

4 DR. WARD: Stan, let me just ask you, are there
5 liquid formulations of Lamisil, if you know?

6 DR. GROGG: No.

7 DR. WARD: Any of these other alternative
8 treatments have a liquid formulation?

9 DR. MATHIS: Fluconazole does, but remember
10 that none of these are approved or tested for safety and
11 efficacy for this indication.

12 Wait. Dr. Nikhar is going to update us on
13 Diflucan, which is Fluconazole.

14 She can speak, just to clarify.

15 DR. NIKHAR: Diflucan was actually studied
16 under a pediatric request at doses of 6 milligram per
17 kilo per day, and Griseofulvin was 11 milligrams per kilo
18 per day for Tinea Capitis, and Diflucan did not win. It
19 wasn't approved against Griseofulvin.

20 DR. ZITO: And that study was conducted by?

21 DR. NIKHAR: The sponsor. It was a pediatric
22 request.

1 DR. ZITO: By the winner?

2 DR. MATHIS: No, it was done by Pfizer.

3 DR. NIKHAR: Pfizer, yes.

4 DR. ZITO: Well, sometimes it is helpful
5 because sometimes there are design modification issues
6 that would lead to a better response.

7 DR. NIKHAR: What I am trying to say is,
8 Griseofulvin was a very low dose and still Diflucan did
9 not win.

10 **Secondary Review of Griseofulvin**

11 **Dr. Jeffrey Blumer**

12 DR. BLUMER: I guess I came away from this with
13 a different conclusion. I had occasion to review
14 Griseofulvin a couple of years ago, and I'm struck with a
15 number of things. First of all, second to Albuterol,
16 this is the most prescribed drug in our outpatient
17 clinic. It is major in our city university hospital.

18 I mean, I have to believe that there is an
19 epidemic of Tinea Capitis out there because it is
20 constant. Every time we go to study something in Tinea
21 Capitis, we can fill these study quotas in about a day
22 and a half. So it is a very, very common problem.

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1 When you look at the literature, there are a
2 zillion papers on Griseofulvin out there and treating
3 Tinea Capitis in kids. I mean, what was provided to us
4 just was the tip of the iceberg.

5 When you track back and see if you can find the
6 basis for the recommended dosing and duration of therapy
7 and whether or not the target populations were ever
8 studied, the answer is, I can't find them. That doesn't
9 say that they don't exist.

10 So in some respects, I come away with a feeling
11 that part of the changes in practice that have resulted
12 in changes in dose and duration are really reflecting us
13 groping to treat this. I don't know that any of these
14 newer antifungals, even though they are fungicidal as
15 opposed to fungistatic, will necessarily offer any
16 advantages. I think part of the difficulty is, we simply
17 don't know how to use these drugs for this indication.

18 I think the uptake and the presence of these
19 drugs into the sebum and into the hair follicles is
20 something that hasn't been fully explored. I mean, there
21 are some data on it and it is an interesting
22 pharmacologic model. How that model then translates into

1 drug efficacy is not at all clear.

2 So I think that there really is a need to look
3 at this. It is a drug that I think pediatricians or
4 pediatric practitioners are in many respects more
5 comfortable with than some of the newer antifungals, but
6 I think that we really don't know how to dose it, how
7 long we need to treat, and what the proper endpoints are.

8 Especially since in urban populations we do see
9 this more in African Americans, I don't know that any of
10 these studies, at least in terms of the pharmacology --
11 certainly, the efficacy studies have been carried out
12 using the target population, because that is sort of who
13 shows up -- I don't know whether the experience in
14 general pediatric practices reflects what happens in
15 dermatologic practices. I would be curious what Dr. Epps
16 has to say.

17 So I think there is a real need to study this.

18 I would give it a high priority, but I almost think we
19 need to start over.

20 **FDA Review of Griseofulvin**

21 **Dr. Roselyn E. Epps**

22 DR. EPPS: I agree with a lot of the comments

1 that have been made. I think there are a couple points I
2 would like to make, also.

3 With the increased immunocompromised
4 population, whether it be HIV or chemotherapy, we are
5 seeing a lot of Tinea Capitis that is not dermatophyte.
6 Griseofulvin and Lamisil are most helpful for
7 dermatophytes. We have a lot of yeast, there are a lot
8 of saprophytes, there are a lot of mixed infections out
9 there. Griseofulvin does not help. That would be one
10 point.

11 Second of all, a lot of times we don't culture.
12 I mean, I tend to do cultures because I'm a specialist.
13 They are referred, it is not working, or something is
14 not right. So we see plenty of Trichophyton, but
15 Microsporum also it is known that you need to treat
16 longer. The standard treatments are not long enough.

17 Sometimes we have to resort to other
18 medications, but obviously, you like to have something in
19 your hand saying this is what I'm treating. You see them
20 back frequently. Sometimes you get baseline lab tests.
21 It is nice to have alternatives.

22 I agree with the previous comments. I think we

1 need to study all of them. I don't think it is simple.

2 Over time even, the causes of Tinea Capitis have evolved.

3 Now we see a lot of Trichophyton species. Before, we
4 had a lot of immigrants; there were a lot of other
5 species. Now we are having other waves with this mobile
6 population. We are seeing all kinds of bugs for Tinea
7 Capitis. So all of it is not the same.

8 I would also advocate the liquid form for
9 Lamisil. I understand that there is one circulating that
10 is not available. That would be wonderful. I think the
11 doses that are published where a lot of times you see 10
12 to 15 per kilo for Griseofulvin, they just aren't high
13 enough. I mean, most people go 20. Some of the
14 pediatricians or some of the dermatologists are going
15 into the 25 range, but you are careful.

16 I mean, you watch those kids, and you don't use
17 it on all of them, or you might get baseline labs just in
18 case, especially if they are on a lot of meds or there is
19 a potential toxicity. You have to see them back, because
20 sometimes six to eight weeks still isn't long enough. I
21 mean, there are some stubborn bugs out there.

22 So I think we need to look at all of them. The

1 Fluconazole, I guess, is the 6 per kilo per day, which is
2 nice. It is a once-a-day thing. It supposedly stays in
3 the skin a little bit longer. It is very helpful. That
4 is also true, I guess, of Lamisil. You can open up the
5 little caplets and sprinkle it on ice cream or whatever
6 the favorite is to get it down.

7 So there are options out there if you have to
8 use other things, but all Tinea Capitis is not the same,
9 number one. Number two, there are a lot of patients who
10 have other issues, and I think we need to look at all of
11 it.

12 Open Discussion

13 DR. WARD: Yes, Stan.

14 DR. GROGG: I would agree with everything that
15 has been said. My suggestion would be that it be studied
16 at the increased dose and the longer duration of therapy
17 for both efficacy and safety and in kids under two years
18 of age, not for the present dose at under two years of
19 age.

20 DR. NIKHAR: Can I say something?

21 DR. WARD: Yes, please.

22 DR. NIKHAR: I heard the previous comments, and

1 I think pediatricians are very comfortable using
2 Griseofulvin. I do think from the division's point of
3 view, we would like to see further dose ranging studies
4 performed, especially in the younger children.

5 DR. WARD: So there is agreement about the need
6 to study Griseofulvin. Great.

7 DR. LAWLESS: Question: How badly did
8 Fluconazole lose?

9 DR. NIKHAR: It didn't win on any of the
10 criteria against any of the bugs. It was actually used
11 in two different regimens for three weeks and for six
12 weeks.

13 DR. MATHIS: Dr. Nikhar, was that a non-
14 inferiority study, or was it a superiority?

15 DR. NIKHAR: Yes, it was a non-inferiority.

16 DR. MATHIS: So it was a non-inferiority study
17 against the 11 milligrams per kilogram of Griseofulvin.

18 DR. LAWLESS: So it wasn't a four-game choke.

19 DR. NIKHAR: I stand corrected. It was a
20 superiority study.

21 DR. MATHIS: Superiority? Thank you.

22 DR. WARD: It may have been an 11-inning game,

1 though.

2 DR. LAWLESS: A question for you, actually,
3 just in terms of, when we make final recommendations
4 later on, you are talking about some of these studies
5 that look like they can be done relatively inexpensively.
6 Some would take a lot more time and effort. Is there
7 going to be a recommendation after this -- and we can
8 talk about this later on -- two drugs versus here are all
9 the ones we reviewed, the top ones, and if we have money
10 left, we do the rest?

11 DR. LASKY: You mean sitting around the table
12 with like poker chips and cigars and horse trading? I
13 don't think we are figuring in the cost right now.

14 DR. WARD: Green eye shades and smoke, yes.

15 DR. SACHS: The only question I have is, in
16 looking at the literature, I didn't get a huge sense of
17 this huge population under three or under two. I was
18 curious from you guys' perspective.

19 DR. LASKY: I just also wanted to throw
20 something out. It is off track, but CDC did recommend a
21 look at Fluconazole. Then, in our review, I think we
22 pulled it out, and I can't remember what the reasons

1 were.

2 DR. MATHIS: It was still on-patent.

3 DR. LASKY: Oh, okay.

4 DR. BLUMER: I would just emphasize that I
5 don't think limiting it to the younger children is
6 important. Just to add some spice to this, we actually
7 had a senior resident for her senior project last year
8 study Griseofulvin, and there were two things that we
9 discussed and were put into the design.

10 One, I was so impressed with the amount of
11 Griseofulvin prescribed that we underwrote doing
12 cultures, and it turned out that 30 percent of the time
13 that someone was prescribed in our clinic -- now, it may
14 be peculiar to Cleveland -- there was no evidence either
15 based on culture or any other evidence that they had a
16 dermatophyte, interestingly enough. So there may be an
17 element of overuse.

18 The other thing was that I did convince the
19 general pediatrician and resident who were doing this to
20 use label doses. In fact, in the study protocol, they
21 got a very high cure rate, which didn't fit with
22 anybody's experience. Now, is it because we are setting

1 them up to use this "forever," I mean, quote, unquote,
2 for two months and they are not taking it at all.

3 I don't know what the answers are, but I am
4 just struck by the fact that this does not seem to work
5 as well as it should, and I haven't a clue why. So I'm
6 not sure I would limit it to these young kids. I think
7 if there is an opportunity to look at it, we really
8 should look at all of the target patients.

9 DR. LASKY: Were those data published?

10 DR. BLUMER: No, they are still in abstract
11 form. I think that they may have been presented at AMP,
12 though.

13 DR. LASKY: It seems like the data need to be
14 looked at carefully before we would go forward.

15 DR. WARD: I think he makes some very good
16 points about not all Tinea is dermatophyte, Dr. Epps'
17 point. I would suspect that many times treatment is
18 undertaken without culture confirmation, and so failure
19 would be anticipated.

20 MS. WOO: The cultures take so long to come
21 back. I mean, I culture all the kids I start, but it
22 takes like two weeks sometimes before you get your

1 cultures back.

2 DR. GROGG: I might add to that culture part,
3 our Medicaid system in Oklahoma doesn't pay for the
4 cultures. I'm told they are extremely expensive and take
5 a while. Thus, we are not allowed to order a culture.
6 That is, I think, silly. But you can't order a culture
7 unless they have been on a course of Griseofulvin for two
8 months.

9 DR. WARD: Back to toxicity, I think.

10 DR. GROGG: We can do KOH preps.

11 [Laughter.]

12 DR. ZITO: I have a question to follow up, Dr.
13 Blumer. Are you alluding to the fact that what we see
14 under research conditions differs from clinical practice
15 experience?

16 DR. BLUMER: I think that is not new,
17 obviously, because it happens all the time.

18 DR. ZITO: Because it is a big problem.

19 DR. BLUMER: Sure, but it is a striking
20 difference because in general practices, those escalated
21 this to two and sometimes even three times what was
22 initially labeled. Why it was initially labeled that

1 way, as I said, I can't discern. Then, the durations
2 just keep extending, so at least general pediatricians
3 seem to be treating for three times as long.

4 So the difference that we generally see under
5 study conditions compared to general practice is now
6 being really amplified in this particular instance.
7 While the safety of the drug is documented, at least in
8 the label it is based on much lower doses. I have no
9 idea what happens when you start dose escalating and
10 exposing patients for this period of time. Obviously,
11 there is not epidemic toxicity that is discernible, but
12 who knows.

13 DR. MATHIS: If I could just add one more
14 point, we have the Diflucan studies that are posted on
15 the Web, I assume, because they were submitted under a
16 written request under the Best Pharmaceuticals for
17 Children Act.

18 So if the Fluconazole is not any better than
19 Griseofulvin and if we know that Terbinafine has a boxed
20 warning for rare cases of liver failure, maybe it is a
21 good option to study Griseofulvin, which we do have some
22 sense that works, and to get just a better idea of how

1 that compares from the safety standpoint as well.

2 DR. WARD: So it sounds like low dose/high dose
3 may be consistent with clinical experience at this point.

4 Yes.

5 DR. WIEDERMAN: Along those lines, I think I
6 noticed on one of Stan's slides a half-life of 24 hours,
7 which would indicate we don't need to give it every day.

8 So that would be Monday, Wednesday, Friday.

9 DR. BLUMER: It sort of depends on what it
10 takes to get it to the target site. The dynamics are
11 complex.

12 DR. EPPS: Certainly, Itraconazole, some people
13 do pulse dose one week out of a month or something, but
14 it is all anecdotal.

15 DR. MATHIS: Poor Dr. Epps has had to deal with
16 a lot of my treatment failures when I did practice in
17 D.C., so she knows. She was always able to cure them.

18 DR. WARD: Shall we move on to
19 Hydroxychloroquine for lupus.

20 Dr. Meythaler.

21 DR. MEYTHALER: I'm not the reviewer.

22 DR. WARD: This has you listed, but if not, I

1 will be happy to discuss that.

2 DR. MEYTHALER: Why don't you go first.

3 **Review of Hydroxychloroquine**

4 **Dr. Robert M. Ward**

5 DR. WARD: At this point, hydroxychloroquine is
6 really only labeled for malarial use in the U.S., yet the
7 preponderance of data are for its use in autoimmune
8 disorders and chronic inflammatory processes: lupus,
9 JRA, chronic interstitial pneumonitis that was reported
10 from Canada from Toronto beginning in infancy.

11 All of these disorders for which this is being
12 used have a small range of dosages. My recollection is
13 they are 4 to 6 milligrams per kilogram per day.

14 Hydroxychloroquine has a retinal disorder that
15 can lead to blindness. It appears to be dose-related.
16 When the dose is exceeded 10 to 15 milligrams per
17 kilogram per day, the frequency was higher.

18 A wonderful group from Cleveland acting under
19 Karen Olness' direction has just completed a randomized
20 control trial for reduction of HIV viral counts in
21 Uganda, and I agreed to serve on their Data Safety
22 Monitoring Board. In that, there were two dosages, but

1 they were 5 milligrams per kilogram per week versus
2 placebo. The code is not broken, but none of the groups
3 has an increased frequency of retinal disorders, which
4 is, I think, a terribly important safety issue.

5 At this point, I think that the issue has to do
6 with, this is a set of very serious disorders: SLE of
7 different forms of cutaneous lupus, more of a renal, and
8 more of a disseminated lupus; and then JRA, Sjogren's
9 syndrome, all of which have been treated successfully
10 with Hydroxychloroquine before they would move on to 6 MP
11 and some of the more potent immunosuppressives.

12 I think this actually is a difficult conundrum
13 because I think it is hard to evaluate and it is not a
14 widespread disease, but it is a terribly serious set of
15 diseases in pediatrics.

16 For that, I thought it actually deserves study.

17 **Secondary Review of Hydroxychloroquine**

18 **Dr. Jay M. Meythaler**

19 DR. MEYTHALER: I'm sorry I wasn't totally
20 prepared, but I do actually have a fair amount of
21 experience in this from my rheumatological days.

22 Hydroxychloroquine has some serious side

1 effects, as a lot of people know, for long-term usage.
2 It causes retinal deterioration and other problems. It
3 can cause some platelet and hematological deficits for
4 long-term uses.

5 Of course, its initial use is in malaria, but
6 it is being used as adjunctive medication in all the
7 rheumatological disorders, so rheumatoid arthritis, SLE,
8 et cetera. It is used as a second-line drug.

9 The studies in pediatrics, I agree with you,
10 are fairly weak. There is some data out there on the
11 drug if you read the material for short-term use for
12 malaria and things like this, but the long-term
13 pharmacokinetics aren't known for people who would be on
14 it for weeks and months at a time.

15 We have no idea how it affects a developing
16 retina. There has been no systematic ophthalmological
17 evaluations of these patients over a long period of time.

18 So there is a fair amount of need, and the drug
19 is used frequently by the juvenile rheumatoid arthritis
20 folks, fairly, fairly frequently.

21 This drug, actually, when I was reading over
22 the material, would, I think, have a fairly high

1 priority. I mean, I did score it fairly high when I was
2 reading over the materials. I think it would definitely
3 rate about an eight on the scale, because it is used
4 fairly frequently.

5 DR. WARD: The rheumatologic disorders are not
6 an area that neonatologists encounter very often, but it
7 appears that there are some very specific antibody
8 monitoring tests that can be carried out to show
9 responsiveness -- I will defer to those in the room who
10 have treated these more than I -- so that the endpoint
11 could be actually fairly distinct.

12 DR. LAWLESS: Are they using it where there is
13 a rescue therapy second-line, or are they using it as a
14 maintenance therapy second-line?

15 DR. WARD: It is more of a rescue, but then
16 they do tend to keep you on it for a long time. Yes, but
17 it is more of a rescue, it is true. After steroids and
18 some of the other things have failed, Hydroxychloroquine
19 is one of the drugs they will use. They will use some
20 other drugs, obviously. Methotrexate has been used, and
21 some of the other immunosuppressants have been used as
22 well, but Hydroxychloroquine has been successfully used

1 in lupus for over 25 years.

2 Dr. Epps and Dr. Zaoutis.

3 DR. EPPS: I agree with the comments so far.

4 We also use it in dermatology for other connective
5 tissues disease, like morphia, scleroderma. Even though
6 eventually they burn out, a lot of people feel it does
7 greatly decrease the course.

8 For those who aren't familiar, it is a kind of
9 hardening of the skin. It can be generalized. It can be
10 asymmetric, and certainly if it is asymmetric like on a
11 leg, there will be a limb length discrepancy and other
12 problems. Sometimes, if it is on the face or the head,
13 you can get seizures or something.

14 So there are some significant sequelae that can
15 occur. Unfortunately, the numbers aren't huge. So it
16 will be much easier to study lupus patients and perhaps
17 maybe translate that over, but it would be nice to have
18 some study period.

19 DR. ZAOUTIS: I don't know the answer to this,
20 but specifically thinking about lupus, the age
21 distribution of lupus patients tends to be older. They
22 tend to be the teenagers. It is the adult data that

1 become more relevant to that population. Is there such a
2 small number of lupus patients that are younger and
3 require specific studies?

4 DR. WARD: This surprised me. I trained in
5 Baltimore and thought I knew about lupus. As young as
6 eight in some of the series, but there were specific
7 manifestations of lupus. They were focal cutaneous sorts
8 of forms.

9 FDA Review of Hydroxychloroquine

10 Dr. Carolyn Yancey

11 DR. YANCEY: Carolyn Yancey from the Anti-
12 Inflammatory Division. Just to add to the comments, I
13 agree with all the different comments. Just on the PK
14 side and dosing, the half-life for Hydroxychloroquine is
15 about 40 days. So it is challenging, and there is no
16 anecdote. So I sort of talk about the risks before I
17 speak to the benefits, which I think are significant. So
18 I'm certainly pleased to hear the initial impressions of
19 the information that people have reviewed.

20 It is used extensively in pediatric
21 rheumatology, specifically for preventing lupus flares
22 and treating and managing the skin manifestations. I

1 would say it is most successful in those two categories.

2 Now, how is that done? We don't tend to think
3 of it as rescue. It is more, maybe, a way to balance a
4 child who is on high-dose steroids where you would like
5 to start to taper those steroids and you need something
6 else that you believe is going to prevent this multi-
7 system autoimmune disease from flaring. That is where it
8 is most successful.

9 In terms of the visual effects, the blindness
10 with this drug can occur. It is extremely rare. What we
11 do in pediatric rheumatology, and I think we have done an
12 exceptionally good job of it with guidelines that were
13 actually collaboratively created from the ophthalmology
14 section as well as the rheumatology section over 12 years
15 ago, we rarely use this drug in children under seven
16 because part of the six-month screening that we require
17 is visual testing, and color vision as well as visual
18 fields. There are some six-year-olds and five-year-olds
19 that can do this, but just as a guide, we rarely use it
20 in kids under seven, but we have definitely used it
21 before.

22 Whenever I have personally seen some

1 abnormality in that six-month screen by a pediatric
2 ophthalmologist, we have either stopped the drug or
3 reduced the dose and it has been resolved. Blindness is
4 reported. I haven't seen that in the kids, and I have
5 definitely seen improvement.

6 Frequent uses, again. For serositis,
7 dermatologic findings, as well as arthritis. It is not
8 usually used by itself. It is usually used in
9 conjunction with something else.

10 One of the studies that was done in the late
11 '70s was Hydroxychloroquine, Dipenicylinide [ph], and
12 placebo. For some of you who have read the literature,
13 they all looked fairly equal. The Hydroxychloroquine
14 performed as well as placebo, and it was a very, very
15 difficult study to explain the results.

16 When you looked at secondary endpoints, and it
17 wasn't quite that rigorously designed at that time, it
18 was most successful for decreasing pain, the arthritis,
19 and the skin findings.

20 The dose is usually once a day. It can be BID,
21 but it is usually once a day. It is usually a dose of 6
22 milligrams per kilogram per day.

Open Discussion

DR. WARD: Would you comment about the use in JRA?

DR. YANCEY: We use it in JRA. We have used it extensively in dermatomyositis, and as Roselyn commented, in other, more rare rheumatic diseases, like scleroderma.

It decreased the thickening and the stiffness of the skin, and that is even harder, I think to even describe anecdotally. But with dermatomyositis, lupus, and then JRA for arthritis as long-term medication. In pediatric rheumatology, we have been rigorous about the eye exams.

DR. WARD: The kids in the study -- I was given permission to discuss this -- they started at six months and went to 12 months, and Dr. Blumer will actually be reporting the kinetics, I think. That is my understanding.

Yes, Dr. Zito.

DR. ZITO: Just a quick comment from a rheumatoid arthritis patient. I have been on this drug.

I have had the eye exams. After about a year, you get into multi-drug regimens, and it really becomes very unclear when you are adding something new.

PERFORMANCE REPORTING

1 So it is curious. My rheumatologist didn't
2 even want me to go on it. I said, "Let's try it. What
3 do we have to lose?" So the adult people, that I'm in
4 touch with anyway, this is like a third- or fourth- or
5 fifth-line.

6 The other concern I have is whether Medicaid is
7 going to pay for that, since someone brought up the fact
8 that some Medicaid systems now are restricting, because
9 without that eye exam, we really set up for a serious
10 risk.

11 DR. WARD: Dr. Sachs.

12 DR. SACHS: I was just curious if there was any
13 data about kidney problems with kids with lupus that get
14 this. Does it help?

15 DR. YANCEY: I don't have data.

16 DR. MEYTHALER: I haven't seen anything in the
17 literature, specifically, with lupus. It is a very, very
18 common problem with lupus, whereas in JRA, juvenile
19 rheumatoid arthritis, you don't get the kidney issues.

20 I do want to state, though, I think it is
21 probably more used in JRA than it is in lupus, and the
22 pediatric population is generally over seven that would

1 develop it. So you see it more frequently used in JRA.

2 I don't know if there is any data with regard
3 to kidney function and how it rescues kidney function in
4 lupus in kids. I didn't find any.

5 DR. WARD: We have several new agents for JRA
6 both in study and recently approved. Are we likely to
7 see a growing use of Hydroxychloroquine, or the same, or
8 decreasing? I will make it multiple choice.

9 DR. MEYTHALER: I think it is decreasing for
10 the reasons that you said, due to the eye exams. It is a
11 pain in the tail to use it, both in the adult as well as
12 the pediatric population. You have to have the eye
13 exams. You can't use it without getting it every six
14 months. It is in the literature. Everybody knows they
15 could get sued if they don't get the eye exams every six
16 months.

17 DR. YANCEY: I also just think in terms of the
18 approval process and the progress, the approval of
19 Methotrexate as well as the increased knowledge and the
20 safety monitoring and when to lower the dose, the ease of
21 titration, the different formulations that allow you to
22 use different administrations, has made a difference.

1 Yes, the eye monitoring is a challenge. I
2 believe the challenge as far as insurance coverage could
3 be overcome without question. There are guidelines from
4 the American Academy of Pediatrics that state very
5 clearly the way in which a person on that medication
6 should be careful.

7 I agree with your point in terms of adult
8 rheumatologists and the approach. Certainly,
9 Hydroxychloroquine is further down on the list with low-
10 dose Methotrexate and Arava. Thought not approved as an
11 indication, it clearly had an acceptable study.

12 DR. MEYTHALER: My one question I have is,
13 Methotrexate is well studied in children, obviously, and
14 particularly with cancers and other things. Some of the
15 other drugs, why haven't they been looked at, some of the
16 other immunosuppressants? Why didn't they make the list
17 as well as Hydroxychloroquine? That is the one thing
18 that caught me by surprise in this.

19 DR. WARD: They may be on-patent.

20 DR. MEYTHALER: Some are, some aren't.

21 DR. YANCEY: A fair question. Lupus, of all
22 the pediatric rheumatic diseases, we are particularly

1 challenged for approved, well-studied drugs for lupus.

2 So it is a challenge.

3 DR. WOODS: I was going to ask, for lupus
4 specifically, it sounds like you want more information,
5 but it sounds like you have very good guidelines for use
6 of the drug, and certainly in JRA or other rheumatologic
7 conditions have a great comfort with the use of it. So I
8 guess one question is, if you had limited resources to
9 study, is this the one you want to have studied for that
10 particular item?

11 DR. YANCEY: I would say we would like to look
12 at the efficacy more clearly. I think on the safety
13 monitoring, we have sufficient information to know how to
14 monitor a child who is taking it, but in terms of
15 efficacy, well-studied information, we really don't have
16 it.

17 DR. MEYTHALER: Would you want to limit this
18 just for lupus or not go to juvenile rheumatoid
19 arthritis? That is the other issue. I mean, that is my
20 question. Why is it limited just to lupus? JRA is an
21 issue, and it is a fairly big issue.

22 DR. YANCEY: Correct.

1 DR. MEYTHALER: So you really need efficacy
2 data more than safety data at this point.

3 DR. WARD: Yes.

4 DR. WIEDERMAN: So, why is our charge to look
5 at lupus rather than JRA?

6 DR. MEYTHALER: I didn't understand that.

7 DR. WIEDERMAN: Aside from lupus, it is mostly
8 adolescents. We all want more information on everything,
9 but that would seem to be low priority. We could
10 extrapolate that adolescent information more easily from
11 adult studies.

12 DR. WARD: I think it is. I think if we feel
13 the greatest pediatric use and gain is in studying JRA,
14 put it in the margin.

15 DR. MATHIS: I would ask Dr. Yancey just to
16 comment on that, too, because it may be an additional
17 study that we want to do.

18 DR. YANCEY: Because of the paucity of approved
19 drugs for adult lupus as well as pediatric, it was the
20 decision of the division to encourage study of
21 Hydroxychloroquine in pediatric lupus.

22 I would agree with expanding the recommendation

1 versus contracting it. It is just amazing to realize
2 what is still not approved for even adult lupus, much
3 less pediatric.

4 Just a comment about pediatric and those that
5 are in big inner city hospitals. There is a huge amount
6 of pediatric lupus in this country. The classic
7 prevalence demographics that you see in adults are
8 different. In children, it tends to be equal between
9 boys and girls. We see four-year-olds with lupus, five-
10 year-olds with lupus, and it is a quite serious disease.

11 DR. WARD: Other discussion?

12 DR. LASKY: Well, I just wanted to say, I went
13 back through the history, and the FDA input does say
14 juvenile rheumatoid arthritis, so there must have been
15 some back and forth on this. I think this conversation
16 is reflecting it.

17 DR. MATHIS: I actually do think that we had
18 been considering all of the options, and then I believe
19 an expert committee wrote in and requested it for lupus.

20 DR. LASKY: I think so, but I haven't been able
21 to find it. So let's look at it as it is and write in
22 the additional one, and we will resolve it.

1 DR. WARD: All right. Dr. Berquist will talk
2 about Sulfasalazine for JRA.

3 **Review of Sulfasalazine**

4 **Dr. William E. Berquist**

5 DR. BERQUIST: It comes right on the heels of
6 the last discussion, so I'll be very interested to hear
7 what the rheumatologists say on this. As a
8 gastroenterologist, I'm very familiar with this
9 medication. This is Sulfasalazine, and the topic,
10 really, is its use in rheumatoid arthritis.

11 What I'm going to do is go through the label,
12 which actually is rather impressive because there is
13 quite a bit of information about it.

14 [PowerPoint presentation.]

15 DR. BERQUIST: This drug actually is two
16 molecules. One is the sulfa part and the diazo bond, and
17 then your 5ASA. The way this works is, you ingest the
18 drug, some of the sulfa is released, which causes a lot
19 of the side effects, and when it gets down to the colon,
20 that bond is broken and releases the 5ASA, which has been
21 shown, at least in ulcerative colitis in adults, to be
22 the agent responsible for its efficacy.

1 Now, as far as pharmacodynamics, the label
2 actually is quite correct in saying we really don't know
3 how this drug works. There have been studies done, but
4 actually, the relative contribution in rheumatoid
5 arthritis in terms of its PD is unknown. It is thought,
6 actually, that this may in part be due to the
7 prostoglandins.

8 In the pediatric population, in fact, it has
9 been studied down to the age of four years. I think one
10 reason for this request is the use of this has been shown
11 all the way down to two years, but there is very little
12 data in the children under four years of age, so to date
13 comparative PK data have not been conducted to determine
14 whether or not there is a significant pharmacokinetic
15 difference between children with rheumatoid arthritis and
16 adults with rheumatoid arthritis.

17 There is a genomic factor, an acetylator
18 status, so 60 percent of Caucasians actually are slow
19 acetylators, which results in a longer half-life. So
20 there is a factor which might result in a higher
21 incidence of adverse effects, so that is a factor that
22 needs to be considered.

1 For indications, it is listed for ulcerative
2 colitis and for prolongation of the remission for
3 ulcerative colitis. It is also used in the treatment of
4 patients with rheumatoid arthritis, and you can see down
5 here it is also indicated for the treatment of pediatric
6 patients with juvenile rheumatoid arthritis who have
7 responded inadequately to salicylates or nonsteroidal
8 anti-inflammatory drugs. So actually, it is on the label
9 for use in rheumatoid arthritis children.

10 Also, it is even more complete at saying when
11 you use it in rheumatoid arthritis you may have to wait
12 for its effect. They even indicate that, and that
13 concurrent treatment with analgesics and nonsteroidals is
14 recommended. So it recognizes that it may take a while
15 for it to work.

16 Now, precautions. Those also go into pediatric
17 use as well, and this is probably one of the key slides
18 that indicates why we are looking at this. The safety
19 and effectiveness in pediatric patients below the age of
20 two years with ulcerative colitis has not been
21 established.

22 Then, in the second paragraph, it goes into the

1 safety and effectiveness for juvenile rheumatoid
2 arthritis, and it covers the ages of six to 16 years, but
3 not under six years. So again, it raises the issue of,
4 how many children are we talking about under six who this
5 might apply to.

6 Again, as far as the extrapolation from adults
7 with rheumatoid arthritis to children, it is based on
8 similarities in disease and response between these two
9 patient populations. Published studies support the
10 extrapolation of the safety and effectiveness for
11 Sulfasalazine for juvenile rheumatoid arthritis.

12 Then they point out some of the problems in
13 juvenile rheumatoid arthritis, including a serum
14 sickness-like reaction. Of course, all of the side
15 effects, which we are well aware of, including fever,
16 nausea, vomiting, headache, rash, abnormal liver test --
17 it doesn't mention colitis, which actually does occur --
18 and treatment of systemic course juvenile rheumatoid
19 arthritis with Sulfasalazine. So if you have this sort
20 of systemic reaction, you don't use it, obviously.

21 So adverse reactions in general. The adverse
22 reactions are similar to those in juvenile rheumatoid

1 arthritis, or the same as adults, including the serum
2 sickness.

3 Also, there is one paper which I will show you
4 about some immunoglobulin suppression in a few patients,
5 and it also includes the dosing for children as well. It
6 indicates, again, how you can actually use the medication
7 but to watch for diarrhea and to sometimes reduce the
8 dose because you can start with a lower dose and
9 gradually increase it. It has the doses for juvenile
10 rheumatoid arthritis listed, and the desensitization
11 regimens have been reported to be effective to cut down
12 on some of the side effects.

13 What we do when we are using this drug is,
14 often, we will start with a low dose and gradually
15 increase it, also watching for any sulfa reactions.

16 So this label is actually quite good and very
17 complete. I might mention there is only one randomized
18 control trial that is listed, and we will try to go
19 through these really quick.

20 The use of Sulfasalazine in rheumatoid
21 arthritis began in adults, and then it was extended to
22 children. This study came from Prague in the early '90s.

1 What they showed was that there was a definite
2 improvement in about 47 percent of their 21 patients, but
3 they also had 19 percent, or four, that had to
4 discontinue. They were comparing it to a hydroquinolone
5 and basically commented right early that there were a lot
6 of side effects.

7 This actually came from another article in the
8 early '90s. There were about four studies in children.
9 It is a little over 100 patients total. Most of them had
10 a favorable response, anywhere from about 40 percent up
11 to 90 percent. Again, side effects in about one-third of
12 the patients on the average. So about two-thirds
13 respond, about one-third have significant side effects.

14 This study here showed a 73 percent
15 improvement. Again, these are all open-label studies
16 sort of following, again, as you would know, what the
17 adults did. The conclusion that it was an effective
18 primary or second-line therapy for JRA and should be
19 studied in a multi-institutional placebo control study.
20 This is 1996.

21 All of these are pretty much similar in showing
22 that there is a high number of side effects with the

1 drug. This shows they are looking at the response over
2 time, showing with time that there is improvement in all
3 of the parameters.

4 Now, there was an Australian multi-center study
5 which looked at 105 patients. These were randomized to
6 coated Sulfasalazine or placebo for six months. They had
7 65 patients, so they had a fair number that dropped out.

8 Again, they looked at a variety of indexes, and they had
9 a lot of side effects as well. There were 14 in the
10 Sulfasalazine and four in the placebo group, and again,
11 had a lot of side effects.

12 This study was the one on immunoglobulin
13 levels. There were six patients, and these five patients
14 here all had low IGA. These had to be less than two
15 standard deviations, and they all got better once you
16 stopped Sulfasalazine. I haven't seen too much of that
17 in the ulcerative colitis group, so I was struck by that.

18 This was the randomized double blind placebo
19 controlled multi-center study from the Dutch multi-center
20 group, and basically they treated with 50 milligrams per
21 day of Sulfasalazine and concluded that it was effective
22 and safe, but it was not tolerated very well in one-third

1 of patients. This was sort of a summary of looking at
2 the various scores.

3 What was interesting to me when I read this
4 paper is that what they did was they looked at the exit
5 outcome and actually did not find a significant
6 difference. It was pretty close, a P value of 0.06, but
7 they couldn't find the difference between placebo and
8 Sulfasalazine until they redid how they scored it, and
9 then they got a significant score. So I thought that was
10 kind of interesting.

11 This shows about how close it is.

12 Anyway, so my comments about this are, when I
13 first read through, I was sort of struck, and as we have
14 talked about it, there are a lot of other drugs available
15 for treatment of juvenile rheumatoid arthritis. I can
16 certainly understand the reason for looking at it. It is
17 just like we do in ulcerative colitis. I mean, this is a
18 horrendous problem to deal with chronic illness and stay
19 away from steroids. So when it works, it is a great
20 drug.

21 I have sort of a love/hate relationship with
22 Sulfasalazine. We are pretty much forced to use that as

1 a first-line drug in ulcerative colitis, and I always do
2 it with sort of trepidation because if I don't do it, I
3 can't use the other options. There are a lot of other
4 options for ulcerative colitis, which I'm surprised
5 haven't been really looked at in JRA, as just a comment.

6 I don't even understand why this drug is even
7 looked at in JRA, except that the adults did it, because
8 if you look at the rationale for it, very little of this
9 drug actually gets absorbed. It is probably about 15
10 percent.

11 So, I mean, from a hypothetical standpoint, why
12 does this drug even work? So in other words, it makes
13 sense for ulcerative colitis because it is released in
14 the colon and there it would have a topical action, but
15 why would it work in JRA is beyond me. At least looking
16 at the studies as I reviewed the literature, I think it
17 is pretty bad. I don't think there really is a good
18 study that shows that this is efficacious.

19 In fact, if I were going to say anything, it
20 might be useful to do an efficacy study. We already know
21 this drug has a lot of problems in terms of its side
22 effects and safety, so if I were going to do anything, I

1 would say, is it really worth anything in JRA, and why
2 don't you spend your time looking at something else.

3 Of course, I am very biased. I would rather
4 see it looked at in terms of ulcerative colitis because
5 that is where we are pretty much forced to try to use
6 this drug.

7 The reason I don't like this drug and I often
8 have a lot of my patients on it is, they get so many side
9 effects, they have problems with colitis that I just
10 cringe to recommend it. I always have to kind of go up,
11 warn people about it, and watch it. So my preference is
12 to try to use it just to see if it will work.

13 When it works, that is the love. It is a great
14 drug for ulcerative colitis. If you can just have them
15 on that alone and not use any steroids. So we at least
16 have these other agents available.

17 I would also urge, if you are going to spend
18 money for something as per our discussion, I would think
19 you would want to put it into Methotrexate or perhaps 6MP
20 or something else, but that is my thought about it.

21 DR. WARD: Dr. Woods?

22 **Secondary Review of Sulfasalazine**

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Dr. Charles R. Woods

1
2 DR. WOODS: As I was reviewing this, I wasn't
3 quite sure whether I was looking at it for inflammatory
4 bowel disease or JRA. One of my questions was, did we
5 actually even have enough information about it in
6 inflammatory bowel disease. It sounds like we could use
7 additional information there if we were going to study
8 it.

9 I don't think I have anything else to really
10 add, except I wonder if some of the side effects during
11 acute inflammatory bowel disease exacerbations, are you
12 more likely to absorb it during severe inflammation, or
13 less likely perhaps? Pharmacokinetic evaluations in
14 those situations might be useful in trying to help use
15 the drug better. I don't know. I didn't see anything in
16 the material to review on that.

17 Just one other minor question I had just in
18 terms of how readily we label anything remotely related
19 to aspirin as needing flu shots. This doesn't have that
20 kind of labeling. Maybe it is not absorbed enough to
21 matter. Maybe we don't need to complicate that further,
22 but I just had that question about the drug as well.

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1 DR. BERQUIST: There is some absorption from
2 the colon. If it gets absorbed at all, it is about 60
3 percent from the colon. Probably once you get really bad
4 colitis, though, you may not absorb anything. It is just
5 exuding, and so probably very little gets in.

6 I think the problem has been that we know there
7 are a number of patients -- it is fairly well documented,
8 although it hasn't been well studied -- that you get a
9 colitis with it, which is really a problem. It is sort
10 of a hypersensitivity. We really don't quite understand
11 that. Once we stop that drug and take them off, we are
12 better able to control their colitis.

13 So there is a need to better understand it.

14 DR. WARD: Dr. Yancey?

15 **FDA Review of Sulfasalazine**

16 **Dr. Carolyn Yancey**

17 DR. YANCEY: Just a few comments. I think it
18 is has been a very thoughtful review, and I agree with
19 all your comments. There is more information in that
20 label than in many, many others that I'm certain the
21 audience has listened to over the last two days.

22 How did it get started. It got started from

1 the initial concept of, is arthritis an infectious
2 process. Would it be beneficial to treat people with
3 arthritis with an anti-infectious agent and an anti-
4 inflammatory agent.

5 There was actually, also, historical learning
6 from gastroenterology that the arthritis that you can see
7 with inflammatory bowel disease improved in those
8 individuals on Sulfasalazine. So the clinical history is
9 quite fascinating.

10 In pediatric rheumatology, we use it most often
11 with reactive arthritis, psoriatic arthritis, which is a
12 real entity, and to some extent in JRA. It is definitely
13 not a first-line agent with JRA, but with reactive
14 arthritis, psoriatic. It is questionable with ankylosing
15 spondylitis in terms of that etiology, which can be very
16 difficult to sort out in that middle age group.

17 The incidence of adverse events is about 30
18 percent in the studies. It is significant. The skin is
19 quite significant. The hypoalbumin anemia, the decreased
20 IGA deficiency, is what we see in the kids with
21 arthritis. I can't explain it, but that has certainly
22 been my experience.

1 Other risk factors. There has actually been a
2 sperm count, if you look at adult studies. In studies
3 five years out in children, and there are not many, it
4 hasn't been an issue, but that is an unanswered question.
5 it definitely is an adverse event risk factor that has
6 to be very carefully explained at the beginning.

7 DR. WARD: That is probably an advantage in
8 teenagers.

9 **Open Discussion**

10 DR. MEYTHALER: Isn't there some question about
11 its transitive effects, too, though? I mean, it doesn't
12 seem to be as long-lasting as Hydrochloroquine or some of
13 the other immunosuppressants in rheumatological diseases
14 both in adults and kids, so consequently, Sulfasalazine
15 is not our first choice for a second-line drug in either
16 population anymore for rheumatoid arthritis.

17 DR. YANCEY: For juvenile rheumatoid arthritis,
18 I would agree it is not first-line. I would say for
19 reactive arthritis or psoriatic, it would be a first
20 line. That is an even smaller population. It is a small
21 population.

22 DR. WARD: Charles.

1 DR. WOODS: One other thought, too, is looking
2 at some of the studies, when they used a 30 milligram per
3 kilogram per day dose, there didn't seem to be as much
4 effect noted as maybe at 50 milligrams per kilo per day.

5 I'm not completely sure those are fair comparisons, but
6 that may get to the issue of how poorly absorbed it is.
7 You don't see as much benefit in rheumatologic conditions
8 until you go to a bit higher dose. That would need to be
9 explored if the drug is going to be used.

10 DR. YANCEY: In terms of prescribing it, the
11 off-label part has been that you have to get to a higher
12 dose. It usually takes about four to eight weeks to do
13 that. To really get an effect clinically you need the
14 higher dose.

15 DR. WARD: Bill?

16 DR. RODRIQUEZ: It is fascinating. If you are
17 here with the process long enough, you see cycles. On
18 December 10, 2002, this drug was brought up to the
19 advisory group. It is fascinating. The division that
20 was suggesting that it be studied suggested ulcerative
21 processes, the colitic process. At that time, it was
22 nixed.

1 It is fascinating that in this meeting we are
2 getting now some of the same feedback that, quote,
3 unquote, we would not have expected in December of that
4 year.

5 DR. WARD: Brownian movement.

6 [Laughter.]

7 DR. WARD: Yes, Dr. Zito.

8 DR. ZITO: Two very quickly. One is what the
9 protocols are within the specialties, and another is what
10 the utilization is in the field. We ought to really pay
11 a little bit of attention to that, or the likelihood of
12 adoption, and so on.

13 The second point, quickly, is that with
14 Zonisamide I think I totally forgot to say something
15 about sulfonamides and their restrictive use in certain
16 populations. I think there has been information
17 suggesting restrictive use in blacks, and I didn't know
18 how much that should affect both of these. At least it
19 is a point to consider.

20 DR. WARD: I think the other point that you
21 made that I think probably would escape many of us is the
22 concern about treating psoriatic arthritis, a disorder

1 that I would not even be aware of.

2 Folks, I think we ought to break for lunch. We
3 will come back and do Cyclosporine, and then have some
4 discussion about the process. Tami needs some feedback,
5 and Don as well, about what has worked, what hasn't
6 worked. I think she may even provide some of the scores
7 from yesterday. We will see.

8 I have 12:30 now. I see the nomination for
9 1:00. One-fifteen, something like that? As soon as
10 people can have lunch.

11 [Lunch recess taken at 12:30 p.m.]

12 + + +

13

A F T E R N O O N S E S S I O N

[Reconvened 1:20 p.m.]

DR. WARD: Not everyone here has scores compared to how we rank things. This, sometimes, disconnect has arisen in discussions about how we will rank drugs for neonates that we have worked on for the last year, and culminated in the meeting in March.

It is difficult to know whether the criteria we are using really select what is more important to study, so we will compare the two ranking systems.

Steve, do you want to talk about Cyclosporine?

Review of Cyclosporine**Dr. Stephen T. Lawless**

DR. LAWLESS: Let's talk about Cyclosporine. Actually, as opposed to a lot of the other drugs, there has been a lot in the literature on Cyclosporine and its use in pediatrics and pediatric transplantation.

In terms of background, Cyclosporine has been purported to be the drug which essentially revolutionized organ transplantation back in the '60s, '70s, and '80s when it was first used.

In terms of the organ transplantation for both

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1 pediatric and adults, instead of having essentially no
2 survival or an occasional survival, we are talking about
3 survivals now in the 80 percent range, 90 percent range,
4 depending on the transplant. The same regimens are being
5 used, whether it is heart, lung, kidney, multi-organ,
6 intestinal, whatever. You name it, they are all there.

7 As part of the regimens of steroids, OKT3 and
8 thiaminositic seroglobulin, and a newer drug, which is
9 FK-506, or Tacrolimus, which essentially is a competitor
10 to Cyclosporine.

11 The reviewers have been asked to look at
12 Cyclosporine against the indication of heart
13 transplantation or its use in heart transplantation, but
14 it is hard to sort out that versus other things. There
15 have been some studies there.

16 In terms of the mechanism of action with
17 Cyclosporine, the real true mechanism is not known. It
18 is excreted in the urine. There are about 15 different
19 metabolites. If you do an assay on it, Cyclosporine does
20 break down, and there is a whole slew of metabolites.
21 Some of them may actually have anti- or may have
22 immunosuppressive properties, but not all the 15 have

1 been fully studied.

2 The absorption of Cyclosporine is both in IV
3 form and PO form. The absorption by PO is very erratic.

4 The newer form has a little better absorption but still
5 has been hindered in terms of the pharmacokinetic and
6 pharmacodynamic data. There has to be a lot of care of
7 how it is given and what medium and what not.

8 In terms of the side effects, there has been a
9 lot written about Cyclosporine, a lot during the studies.

10 Even though the label hints that there have been studies
11 done in pediatrics, there just are not well done
12 pediatric studies. It is not that they have not been
13 done, it is just kind of declarative.

14 The side effects, however, are pretty
15 significant. One of the reasons why it is written up so
16 much is because of the side effects. They are not hard
17 to find. Anywhere from giving an agent which is very
18 nephrotoxic for kidney transplants. Hypertension is a
19 severe problem. Having thrombocytopenia with a
20 hemolytic anemia reaction and thrombosis is a problem.

21 Some electrolyte abnormalities, seizures,
22 encephalopathy, mostly with higher levels of

1 Cyclosporine. Rare cases of anaphylaxis.

2 The two big things are actually hirsutism and
3 gynecomastia, which may not seem like much, but in
4 adolescents, they are probably the two biggest reasons
5 why adolescents stop their medicine. It is hard to get
6 prom dates when you have hair all over your body. That
7 issue is a real issue for a lot of them. They will stop
8 taking it for those reasons.

9 The other thing, actually, is that in terms of
10 the dosages, even though the pharmacokinetics have been
11 really worked out, a couple of things which are trouble
12 or hard with this are that there are multiple ways of
13 passing Cyclosporine. You can do it by HPLC or
14 radioimmune assay, and depending on the conditions you
15 are using, the levels of the serum or plasma levels have
16 to be interpreted in different ways.

17 Most immunologists also gear towards levels,
18 aiming for a certain level, rather than saying, we can
19 give this dose and walk away from it. They will measure
20 sometimes twice a day the levels initially of
21 Cyclosporine to balance out to a certain level.

22 I think the interesting thing, and one of the

1 reasons for the heart transplantation study in particular
2 -- this is going back a little bit to my days in
3 Pittsburgh -- were that, depending on the transplanted
4 organ, you were aiming for higher levels of Cyclosporine
5 because you would think that if you had a kidney
6 transplant, you could aim for lower levels in the long
7 term, less nephrotoxicity, less side effects. You can go
8 back to dialysis if you have to.

9 Liver transplantation, a little bit more
10 intermediary. However, for heart transplantation, they
11 were going for higher levels. So at higher levels, you
12 have a higher incidence of having side effects, including
13 nephrotoxicity.

14 However, the studies on what is the optimum
15 level versus rejection are not as easy to come by,
16 because even though some of the articles submitted said,
17 here is a table which says nephrotoxicity or organ damage
18 from Cyclosporine versus rejection, which is the thing we
19 worry about, trust me, it is not as easy as determining
20 one has vacuoles, one has inflammatory reactions. You
21 can have five pathologists look at the same slides and
22 come up with different answers. It is a very, very

1 difficult thing.

2 So there are various different ways of doing
3 it. Some people avoid IVs, some people give the IV. A
4 lot of problems with conversion from IV to PO and
5 balancing things. Sometimes the therapeutic window is
6 narrow and sometimes the therapeutic window doesn't seem
7 to be narrow. So it is not an easy drug to play with,
8 though it is very popular.

9 Now, adding on top of that, you have FK-506
10 now, which has become also very, very popular.
11 Essentially, it is the competitor. You don't use
12 Cyclosporine and FK-506 at the same time. It is one or
13 the other.

14 FK-506, in most of the studies shown, has been
15 used in kids. Some of the articles reference double
16 blind studies done, randomized clinical trials done in
17 pediatrics, though not on the summary sheets.

18 It seemed to have less side effects than
19 Cyclosporine, but the trouble is that there is also some
20 evidence that FK-506 causes more nephrotoxicity. So
21 there is a little bit of a question mark there.

22 Now, on top of that is the reason why, also, it

1 is important to look at this from the short-term, which
2 is preventing acute and hyperacute rejection. There is
3 also the new long-term issue which is coming out, which
4 is that it was initially thought that kids who got the
5 transplant at the same time they got introduced to either
6 Epstein Barr virus or CMV had a lympho-proliferative
7 disorder that would develop, post-transplant lympho-
8 proliferative disorder, which was responsive to taking
9 away your Cyclosporine. You would get better from it,
10 but then you would reject.

11 So you have this balance, and sometimes it
12 would become malignant. The incidence initially was
13 about 0.4 percent a year when they were sort of
14 discovering this event.

15 The trouble is, it is every year. It is
16 cumulative. So there is about a 1 percent chance of
17 getting this every year. So now that you are seeing
18 survivals of 10, 15, 20 years, now you are seeing about
19 20 percent incidences of lympho-proliferative disorders
20 popping up in these kids, and in adults, too. So there
21 is the short-term toxicity and now there is the long-term
22 toxicity coming up, also.

1 Now, initially, when I reviewed this, when I
2 reviewed this, my recommendation was a high score,
3 thinking they have a lot of data here, a lot of studies
4 done. Yes, we should study this, this is a big
5 population, big push for organ transplantation,
6 especially because it is now being used in things like
7 the nephrotic syndrome, arthritis, a lot of off-label
8 stuff. People are trying to use it, just trying to go
9 for lower levels.

10 There is a lot of data out there which hasn't
11 been really compiled into almost like a summary
12 statement. This is what we think should be done.

13 The New England Journal had an article in its
14 infancy on Cyclosporine, which is still probably the best
15 article ever written on Cyclosporine, and it was 20 years
16 ago.

17 The problem is there that all these new
18 problems are popping up and you have these new drugs to
19 play with. I gave it a high recommendation for study
20 because it is such a difficult drug and people are
21 actually flying by the seat of their pants a lot of times
22 with it. It is a dangerous drug, but it can also be a

1 very, very powerful drug.

2 DR. WARD: Would you characterize those limited
3 pediatric studies? Are there RCTs in that, or are there
4 various ages?

5 DR. LAWLESS: Actually, yes. Actually, I was
6 surprised because I was looking at some of the articles.

7 They were even describing RCT in a heart transplant. So
8 when you are comparing Tacrolimus versus Cyclosporine,
9 which is the only way you really can compare it because
10 it wouldn't be steroids versus non-. I mean, it has to
11 be something to something.

12 They said in terms of efficacy of
13 immunosuppression and rejection, they are probably equal.

14 The Cyclosporine has more side effects overall than the
15 FK-506 because it still has the same incidence of
16 leukemia and lympho-proliferative as Cyclosporine. So
17 there is a choice now working with that. A study would
18 almost be a hand-in-hand.

19 There was a mention of some of these studies,
20 but they weren't summarized, necessarily, in the overall
21 picture that I got.

22 DR. WARD: Bill.

FDA Review of Cyclosporine

Dr. William E. Berquist

DR. BERQUIST: Thank you.

I am very familiar with this drug because I have had to deal with it since 1984. I think we talked about this last year, too, if I'm not mistaken.

There actually is a lot of work on pharmacokinetics. Pharmacodynamics, there is also a lot of work. We do understand the calcium inhibitors work in a particular area in terms of the immunology to decrease IL2, and so there is a calcium binding protein for Tacrolimus, or FK-506, there is also a separate binding protein.

What we really don't know is we don't know what really induces tolerance and how to sort of monitor it from an end target. So we end up measuring drug levels of Cyclosporine as well as Tacrolimus to sort of guide us as to how to use it.

I think most people in transplant are very familiar with the toxicities, and most organ transplant groups have moved away from Cyclosporine. If you look at the data split in these studies in Pediatric Liver

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1 Transplant, which I am a member of, we looked at the
2 trend in liver transplantation, and you see a shift from
3 all the centers using Cyclosporine over to Tacrolimus.

4 The reason for it is really the side effects of
5 toxicity as well as the efficacy of the drug. So the
6 reason that Tacrolimus got approved for use in children
7 in liver transplant is they did a large study comparing
8 it against Cyclosporine.

9 So the fact is, we have a lot of data already
10 for Cyclosporine in kids in terms of why we are using it.

11 In talking to the cardiologists, which I recently did.
12 I talked to those at UCLA, where they are not using
13 Cyclosporine anymore for their heart transplant patients.

14 They indicated to me that most of the cardiac transplant
15 groups are still using Cyclosporine.

16 So I think the reason this was chosen, if I'm
17 not mistaken, is that you have a few groups that haven't
18 moved over in part to using Tacrolimus, and so that may
19 be one impetus for it.

20 The other issue is, Cyclosporine, as you know,
21 is now off-patent. So there are some questions which
22 would put it under the purview of this prioritization

1 process. Most of the issues that I think have been
2 talked about, including PTLD, are big issues. Actually,
3 with the monitoring that is done now and with the
4 antivirals that we use, we had an incidence where we were
5 in around 15 percent, especially in intestinal
6 transplant.

7 In cardiac transplant, where you run very high
8 levels, again that is kind of a learning you do in
9 transplantation. You take the risk of these
10 complications and you learn how to do it. I find our
11 cardiologists a lot of times seeing their patients with
12 really bad CMV, occasionally PTLD. I think if you do the
13 right protocols, there is a good body of knowledge of how
14 to manage that.

15 So we have cut down on the degree of PTLD,
16 especially in liver, and it may be more difficult, say,
17 in heart transplants. It is more of a problem, actually,
18 with the Prograf, which I think has a greater risk of
19 causing PTLD, but it was first reported with
20 Cyclosporine.

21 It is sort of like, well, what is really the
22 question. The question is Cyclosporine for heart

1 transplant. You don't need that. We know it is used for
2 that. They already have it.

3 So I think the question has more to do with
4 understanding some of the safety issues long term, not
5 efficacy. We know how effective the drug is, so I think
6 that if we were going to study anything -- and this would
7 not just be for heart transplant, it would be for anybody
8 using Cyclosporine on a very, very long-term basis --
9 what kind of studies would you do. As you know, that is
10 kind of a tough area.

11 We also know Cyclosporine has an effect on
12 mitochondrial function, so it turns out it may have a
13 role in learning problems and there may be some other
14 areas that we are not looking at long, long term.
15 Remember, these kids are stuck on this drug basically
16 their whole life and they have to keep a certain level.
17 They are running into these side effects.

18 So I can understand why we might want to look
19 at some of the long-term toxicities, but I think you have
20 to start narrowing down the focus of what the question
21 is. Are you going to look at learning problems, are you
22 going to look at kidney problems, are you going to look

1 at PTLD, and are you going to have enough patients to be
2 able to do that.

3 I think, in a way, the attention is moving away
4 from Cyclosporine and moving towards Tacrolimus, but that
5 is, I believe, still on-patent.

6 **Open Discussion**

7 DR. WARD: Let me ask the superficial question.
8 What is the age range for labeling at this point?

9 DR. LAWLESS: For cardio transplants, it is
10 infancy up, actually, newborns or first month.

11 DR. WARD: I wasn't sure whether we had taken
12 that step to get a label down to neonates.

13 Bill, it sounded like your major question would
14 be one of long-term outcomes and toxicities that may not
15 be identified yet.

16 It sounds like both of you have said that the
17 link between efficacy or effectiveness and concentration
18 may be not as tight as we would like.

19 DR. BERQUIST: Again, I sort of reviewed this
20 last year. We really looked at the PK data, and that has
21 really been well done in kids. I think there are some
22 excellent reviews on that, and a good knowledge of some

1 of the moderate, even somewhat long-term safety issues,
2 is how better to kind of deal with that.

3 DR. LAWLESS: The PK is good. I agree 1,000
4 percent.

5 PARTICIPANT: That is a lot.

6 [Laughter.]

7 DR. LAWLESS: I was going to say 1,000 percent,
8 but.

9 [Laughter.]

10 DR. LAWLESS: The only clincher is that you
11 still end up with the management of the transplant
12 surgeons. At 4:30 in the afternoon the Cyclosporine
13 levels or the FK-506 levels are back, do we leave them
14 alone; add 10 percent, 5 percent. So it is a lot of the
15 seat-of-your-pants type of a thing. So it is more like
16 clinical pharmacodynamics you are trying to link to. If
17 the kid's fever is up or has a fever, let's adjust and
18 play with it.

19 So the pharmacokinetics are good because you
20 can get it to the level you want, but it is the
21 management of, now what do I do if the clinical situation
22 changes.

1 DR. BERQUIST: To me, that is like Transplant
2 101. I mean, you have to do that stuff. If you don't,
3 your program isn't going to do well. So to me, that is
4 kind of a basic thing.

5 The thing that is strange in the label -- I
6 just wanted to comment on that -- is the label actually
7 says not to use a second immunosuppressant agent with
8 Cyclosporine. I don't understand that. I know where
9 that may have come from before, but one way we are using
10 this is to actually lower the dose of Cyclosporine and
11 use a second agent. That actually allows us to run
12 fairly low levels, decreasing the renal toxicity, because
13 you can use Rapimmune or you can use MMF.

14 That is a little bit of a problem that I have
15 with the label.

16 DR. WARD: We will turn it to Dr. McCune. You
17 can answer that.

18 DR. McCUNE: No, I can't answer that. I
19 totally agree with that. I think a lot of the literature
20 has advanced since the time of the label in terms of
21 combination therapies in order to do exactly what you are
22 saying, which is to decrease the steroid load and to

1 reduce the risk of renal disease.

2 I also wanted to clarify a point about
3 labeling. Although we are using it in transplant
4 patients that are in the neonatal period, the label
5 actually says that there are no adequate and well
6 controlled studies conducted in children, but patients as
7 young as six months of age have received the drug with no
8 unusual adverse effects. So in theory, it is really only
9 down to six months in the label.

10 I just wanted to add a couple of points. In
11 addition to the Tacrolimus, we are now getting a number
12 of other agents as well: Sarolimus and Everolimus, I
13 guess it is. There are three current trials that are
14 ongoing in pediatric patients with renal transplant with
15 those agents.

16 I think that this drug wound up on the list
17 this time for a couple of reasons, although heart
18 transplantation was the indication that you all looked at
19 it for. I also believe the reason why it is in with
20 those other two drugs that you just discussed before
21 lunch was that the Anti-Inflammatory Division had also
22 wanted it discussed from a rheumatologic perspective and

1 for its potential rheumatological use. I think Dr.
2 Yancey can probably speak a little bit more to that.

3 DR. WARD: Does it correct obesity?

4 [Laughter.]

5 DR. MATHIS: Lice. If it deals with lice.

6 PARTICIPANT: It takes away the side effects of
7 Clonidine.

8 [Laughter.]

9 DR. YANCEY: There are very, very, very few
10 pediatric rheumatology trials with Cyclosporine. The
11 only ones I have been able to find have been open-label
12 and anecdotal. It has been successful. It is usually
13 used with very sick children who are recalcitrant,
14 resistant to everything else.

15 In the Anti-Inflammatory Group, we are
16 proposing that this be studied in children with pediatric
17 lupus. Again, there are very, very few drugs approved
18 with a specific indication for lupus in adults or
19 children, but I would urge consideration of this for
20 pedes lupus.

21 DR. MEYTHALER: There is a fair amount of work
22 going on in the adult side that hasn't come down to the

1 kids, but it is being used hugely now in neuroimmunology.

2 It is being used in CIDP, other inflammatory neuropathy
3 issues. I just came out of Neurotrauma and Neuroscience,
4 and they are looking at it in Neurotrauma in general. It
5 may be protective against neuroimmunological effects in
6 acute head injury, spinal cord injury, et cetera. There
7 were at least six posters and about two presentations
8 last Thursday and Friday on this drug, so its use is
9 going to expand very rapidly.

10 DR. BERQUIST: That is a very interesting use
11 of it. As I mentioned, it affects mitochondrial
12 function, so it actually --

13 DR. MEYTHALER: Caspase pathways. It affects
14 the caspace pathways, yes.

15 DR. BERQUIST: So there are these other actions
16 which we are beginning to become aware of, but they may
17 have other importance in terms of learning and other
18 kinds of function.

19 I'm just surprised, if you are going to pick a
20 drug for immunosuppression, I mean, we have moved away
21 from Cyclosporine and moved towards Prograf.

22 That is my thought about it. I guess it is

1 reasonable to study Cyclosporine.

2 DR. LASKY: I just wanted to throw out that the
3 American Heart Association asked us to take a look at
4 Cyclosporine for heart transplant patients but didn't
5 provide any other information. They listed about 10
6 drugs and conditions.

7 The other comment that I had is that in taking
8 a quick look at the literature before we sent it out, it
9 looked like many of the RCTs were for kidney transplant
10 patients but not much for heart transplant patients.

11 This seems like a good situation where we would
12 want to do a meta-analysis of the kidney transplant
13 literature and then take a look and see what can be
14 extrapolated to the heart transplant situation and what
15 can't be.

16 DR. LAWLESS: I think there were a few. At
17 least one I know of. I saw one reference in one of the
18 articles on heart transplant in particular with kids.

19 DR. McCUNE: Yes. We looked at both, and there
20 really wasn't a substantial difference between the two,
21 and the recommendation being, if you are a transplant
22 center that prefers Cyclosporine and you are used to it

1 and you know how to monitor it, don't change horses in
2 midstream. If you are not, you can develop your program
3 with Tacrolimus.

4 DR. BERQUIST: Again, this is the phenomenon we
5 see in kidney and we see it in liver. In intestinal
6 transplant, they tried to use Cyclosporine, and that is
7 where, I guess, it becomes very obvious. Cyclosporine
8 was really tried at the very beginning and was very
9 unsuccessful. So all of intestinal transplantation now
10 is done with Tacrolimus for that very reason. So it is
11 just not as effective an immunosuppressant agent.

12 DR. LASKY: The point I wanted to throw out is
13 that perhaps we need an intermediate step of this more
14 systematic review of the literature before deciding to
15 undertake what would be an extremely challenging and
16 expensive clinical trial.

17 We don't have this option on the paper, so I'm
18 throwing it out for the column, but it just seems like we
19 need to look at the literature in a very careful way.

20 DR. WARD: It sounds like both of you have
21 indicated it is fairly extensive, especially in renal
22 transplants.

1 Dr. Epps and then Dr. Zito.

2 DR. EPPS: Just to piggyback on some earlier
3 comments, we use Cyclosporine anecdotally in dermatology,
4 also, for erythrodermic psoriasis, things where topical
5 things aren't options, or severe recalcitrant atopic
6 dermatitis.

7 Anecdotally, I don't know how it would fit into
8 your study issues, but it seems at times that the generic
9 is not the same as the trade. I would presume those
10 studies were done at some point, but in talking to some
11 colleagues, when the pharmacy switched them over, you
12 have an erythrodermic hospitalized kid because the levels
13 are zero. Whether it is an absorption issue; I don't
14 know what the issue is, but in different fields, people
15 have mentioned the same incident.

16 DR. BERQUIST: It is really an absorption
17 issue. Again, in transplantation, we have already
18 learned that. I guess a lot of people are not aware of
19 it, but we really have to monitor those levels, and that
20 is a given responsibility. When you are using this drug,
21 you need to know that and you need to know how to use the
22 drug.

1 DR. EPPS: I'm saying it is a pharmacy issue as
2 well.

3 DR. BERQUIST: Right. We are aware of it. It
4 might be a thing you could study, brand versus generic.

5 DR. EPPS: That was my point.

6 DR. WARD: Have you had the same experience Dr.
7 Epps describes from a proprietary to a generic?

8 DR. BERQUIST: Oh, yes. The San Francisco
9 Chronicle had a wonderful article about that.

10 DR. WARD: I'm sure it is in the bibliography.

11 [Laughter.]

12 DR. WARD: Yes, Dr. Zito.

13 DR. ZITO: I was just sitting here wondering
14 about registries or about organizations in which all the
15 transplant people talk to each other, because a quick and
16 dirty survey would shed a lot of light on who is using
17 what and what the need is.

18 DR. LAWLESS: It is not like a CCSU or a POG
19 [ph], where here are the protocols you really know and
20 you are really tracking this thing diligently. It is
21 more of a registry with a lot of political overtones to
22 it.

1 But if it had more of a structure like a CCSU
2 or a POG or something along those lines, or the Cambridge
3 Study Group, then you would be able to do this very, very
4 nicely.

5 DR. WARD: Frankly, a survey about dosage
6 ranges and concentration ranges used and outcomes could
7 be beneficial.

8 DR. BERQUIST: Just so you know, I mean, there
9 are some organizations that can help facilitate various
10 studies. I don't know what they have in heart, but there
11 is Naportex [ph] for kidney and split for liver.

12 So what we are doing in transplantation is sort
13 of getting together, just like oncology or other areas,
14 so we can look at various protocols to sort of make that
15 easier to kind of do multi-center trials.

16 So we have a database. This actually is NIH-
17 funded right now. It is the SPLIT database. So we have
18 39 centers which are contributing.

19 I think that transplant is trying to develop an
20 infrastructure, so it may be the kind of thing you could
21 come back and say, well, we would like you to do such and
22 such, as well as have a dialog.

1 DR. ZAOUTIS: There is a pediatric database as
2 well.

3 DR. WARD: For hearts. I know there is a JRA
4 multi-center trial group.

5 Is there anything related specifically to lupus
6 that brings people together?

7 DR. YANCEY: Lupus is covered in two
8 collaborative groups, the Pediatric Rheumatology
9 Collaborative Study Group, which has been in existence
10 longer, but the second group, CARA, Childhood Arthritis
11 Rheumatic -- I forget the acronym, but there are two
12 groups, and yes, lupus is definitely covered.

13 DR. WARD: I think usage as well as a little
14 bit more detailed information about the relationship
15 between outcomes and concentrations and your style of
16 management gives us at least a range to shoot for as
17 well.

18 DR. BERQUIST: Again, it comes from what is the
19 PD. I mean, we know the PK. The question is, what is
20 the PD. What you end up doing in transplant is cause and
21 effect. If they are not rejecting and you can use a
22 lower dose, then you have less side effects.

1 That took a long time. It was this curve that
2 you had when you first got that drug that came out.
3 People had all kinds of disasters. You learned from it,
4 and gradually you achieved what tended to be a standard
5 trough level.

6 That is really the criticism, that as you get
7 farther out, can you lower that trough level and cut down
8 on the long-term side effects. That may be the area to
9 focus on.

10 DR. MATHIS: Do we also need to focus in on
11 where the drug is used with another immunosuppressant,
12 like Tacrolimus. Do we need to look at it in conjunction
13 with another drug?

14 DR. BERQUIST: Probably not with another
15 calcium inhibitor, but that would be another thing I
16 think would be very good, is to cut down on the
17 nephrotoxicity by using it with either Rapimmune or
18 Sarolimus and Mycophenolate mofetil or CellCept. So I
19 think you could use those.

20 DR. WARD: Do you see any problems with biliary
21 problems in your patients? You are in the liver
22 transplant group.

1 DR. BERQUIST: Biliary?

2 DR. WARD: Yes, with Cyclosporine.

3 DR. BERQUIST: Not really, because most of ours
4 are biliary atresia. They don't have a biliary tract.

5 DR. WARD: Okay.

6 [Laughter.]

7 DR. WARD: I was curious.

8 DR. BERQUIST: But actually, you don't. There
9 is an issue about bile flow and absorption.

10 DR. WARD: Yes, biliary stasis.

11 DR. BERQUIST: So that is a big factor in terms
12 of absorption, yes.

13 DR. WARD: Go ahead.

14 DR. HERNANDEZ: My name is Arturo Hernandez
15 from the Immunologic Drug Products, FDA. I have just a
16 couple comments.

17 I mean, registry data show definitely that the
18 transplant community, which is the one that we have more
19 experience with Cyclosporine, is moving from Cyclosporine
20 to FK, the alternative calcium inhibitor.

21 For me, it looks like in all the kind of
22 transplants, which reflects also what is happening in

1 pediatric patients, more than 60 percent of the programs
2 are using FK, with the exception of heart transplant,
3 which approximately 60 percent are using Cyclosporine.
4 The rest are using FK.

5 So for me, we just have two alternatives for
6 calcium inhibitors. There is FK or Cyclosporine.
7 Cyclosporine has been on the market since the early '80s,
8 '72, '74. We know a lot about Cyclosporine, so for me,
9 it makes sense.

10 The trends in the scientific registry point to
11 that approximately I would say in five or 10 years we
12 will see the usage of Cyclosporine, at least in
13 transplantation, is going to be a minimum. As you said,
14 for example, the units are using FK in all transplants, I
15 mean, at least in the areas of major transplant centers
16 such as Washington Hospital Center in Fairfax and
17 Georgetown University. They are using predominantly FK.

18 So for me, it makes sense if we are going to
19 spend any resources to try to learn a little bit more
20 about how to use the drug in kidneys. We have two
21 alternatives, either FK or Cyclosporine. It would make
22 even more sense to use those resources in trying to learn

1 a little bit more about FK.

2 DR. WARD: Other discussions?

3 [No response.]

4 DR. WARD: I would ask you to score these
5 sheets that were sent out, Task 1 and 2 as well as the
6 three Sheets 4, 5, and 6 from today. We will pick those
7 up if you lay them out.

8 Tami, do you want to go ahead and discuss the
9 good, the bad, and what we need to do differently.

10 **Summary of Day 1**

11 **Dr. Tamar Lasky**

12 DR. LASKY: Well, yesterday I said I wasn't
13 going to thank anybody until after I saw what kind of job
14 everybody did, so now I can say thank you all so much.
15 You did a fantastic job.

16 Thanks, first of all, to the members of the
17 Expert Panel. You just did a great job in your areas.
18 You did a great job of being able to think about
19 questions that were outside your areas. You have been
20 very supportive as we go through our developmental
21 stages.

22 I think our first two years we were in our

1 infancy, and this year we are in our toddlerhood, so if
2 you are patient, we will grow up and mature and we will
3 have a great process and great impact on pediatric health
4 over time.

5 Thanks to Bob Ward for serving as chair. You
6 did a great job. You kept us on task and on schedule.
7 We want to renew our contract with you for the same high
8 rate of pay.

9 [Laughter.]

10 DR. LASKY: Maybe we should give him a raise.

11 DR. WARD: Right. Make it double.

12 DR. LASKY: We can't afford a raise, but we can
13 give him a lot of job security.

14 [Laughter.]

15 DR. LASKY: Thanks to the FDA and NICHD members
16 of the working group who met over the different months
17 and helped hash this out. They are all seated at the
18 table.

19 I wanted to thank my boss, Don Mattison, who is
20 the branch chief and the leader of all these activities,
21 especially for his perfect mixture of sound advice and
22 support and a little bit of neglect in there. That just

1 works out perfectly.

2 The contracting people did a great job. They
3 are not here to hear our thanks, but we are glad that we
4 had support there.

5 Thanks to everybody who attended and
6 participated, and who care about this process.

7 Before we get to the discussion of next year's
8 process, or maybe by way of bringing us to that
9 discussion, last night I couldn't resist. I was taught
10 in graduate school never to take peek-looks at the data,
11 to bring it all back, clean it, review it, and do all
12 this stuff, but I didn't follow the teachings that were
13 given to me. I did take a look at the data, and I really
14 wanted to share them this morning.

15 I have a preliminary tabulation of the drugs we
16 reviewed yesterday. We will see what people think of
17 them. I'm not sure what I think of the whole thing.

18 [PowerPoint presentation.]

19 DR. LASKY: This is how it worked out. I
20 scored it this way. I tallied up the marks that were
21 given for study for the drug in 2005 in one column.
22 Then, in a second column, I tallied the recommendations

1 for study of that drug a year later.

2 So in my quick and dirty look with no
3 statistics, it looked like either way we look at it, just
4 looking at the first column or the second column or the
5 two combined, we get the same drugs being at the top of
6 the list.

7 I have the on-patent drugs in a separate
8 category, but in the off-patent drugs, there was a lot of
9 unanimity. Hydrochlorothiazide for hypertension, and you
10 can read this.

11 If we go down the list to Flecainide, you have
12 plurality, or a majority of the experts recommending it
13 for study. Then, below that, we have a little weaker
14 recommendations and support.

15 As I said to Bob earlier, I'm going to compare
16 this to how the scores worked out on the sheets and see
17 if there is any logic here or if we could just next year
18 save money and just do like some Monte Carlo imputation
19 and just generate like a random set of numbers.

20 [Laughter.]

21 DR. WARD: The wrong Monty. It was Python.

22 DR. LASKY: Monty Python, yes. That would be

1 good.

2 [Laughter.]

3 DR. LASKY: These are very small numbers, but
4 people clearly think the on-patent drugs are important to
5 study. It is something we are going to have to bring
6 back to our congressional liaison and all of our
7 policymakers.

8 People want us to study the on-patent drugs, in
9 addition to studying the off-patent drugs, but there was
10 very strong support for the study of Morphine for
11 analgesia and for Bupriopion for depression, a little
12 weaker for the smoking cessation.

13 So those were the peak results for yesterday,
14 and of course, I don't have today's. I will probably run
15 home and do that right away, but we can use that when we
16 are discussing.

17 **Plans for the Coming Year**

18 **Dr. Tamar Lasky**

19 DR. LASKY: This will just take a couple of
20 minutes. I will talk a little bit about what plans are
21 in the works, and then we will just have an open
22 discussion. I think I will ask Bob to moderate the

1 discussion.

2 [PowerPoint presentation.]

3 DR. LASKY: This is a diagram of what the
4 process was this year and the input we put into it this
5 year and what we are planning for the coming year. It
6 just seems to have turned out that we have divided the
7 year into these quarters: February to April, which is a
8 kind of outreach period of time where we are sending out
9 the mailings, soliciting comments. This is when we
10 receive the suggestions for the drugs and indications.

11 Once we got that material in hand, it does take
12 a certain amount of time to sift through it and sort it
13 through and incorporate it into whatever we are using, a
14 spreadsheet or now we have a database set up to keep
15 track of this and review the comments, rank it, and have
16 a preliminary list.

17 So for people who are interested in having
18 input in the process, and if you know other people, this
19 is the time to really get the information to us. Anytime
20 it is welcome, but February to April is especially
21 effective.

22 This year, we published the preliminary list in

1 the August Federal Register, and from that time forward,
2 we planned for this meeting. That is not a good time for
3 input because we are trying to process the material.

4 This year will be our first time with this
5 process. We will take the information from today, we
6 will summarize it, we will look at it, we will discuss
7 it, and we will see how it looks and what we are able to
8 do. We will consider what things are feasible, what
9 things are expensive, how it cuts across different
10 disease groups.

11 I have gone over the middle column of the
12 material we brought in. Actually, the two last boxes are
13 really going to bring this input into next year's
14 process, because we haven't gotten the results yet. We
15 are going to have information on hospitalizations. We
16 are going to have the Maryland Medicaid Outpatient
17 Frequency of Use, and we are going to have some inpatient
18 data from Dupont. That will go into next year's process,
19 which will repeat.

20 We may do the outreach exactly the same; we
21 might change it. That is one of the things we need to
22 discuss, what changes would we make this year.

1 We are going to have many more literature
2 reviews, more substantive literature reviews, and we have
3 already set aside 12 drugs that had an abundant
4 literature that did not reach the process this year
5 because we felt it was necessary to have literature
6 reviews. They should come to the process next year
7 because we will have invested so much in studying them at
8 least from a literature point of view.

9 There will be more data coming in from RTI on
10 the frequencies of condition and from Westat on the
11 frequencies of outpatient use. It might, again, in that
12 last quarter, really feed into the following year
13 process.

14 So we are really putting an emphasis on
15 increasing our knowledge base, continuing to increase our
16 knowledge base, but this time we are also going to try to
17 look for areas in the literature that we can feed into
18 the labeling process and save time and money for these
19 other areas in which we can't rely on the literature.

20 These are some of the activities underway. We
21 are finishing a purchase order with the University of
22 Maryland, this interagency agreement with the Agency for

1 Health Research and Quality, a purchase order with
2 Dupont. We are going to have a colloquium on November
3 9th and start to talk about inpatient use, because that
4 was missing this year. It is much more difficult to
5 obtain.

6 We are just beginning a contract with RTI
7 looking at the frequency of conditions. The project
8 director is in the audience, and she has been taking
9 notes of all the conditions we are interested in, all the
10 lice, all the skin conditions, and everything else we
11 have talked about.

12 Westat is going to go beyond the Express
13 Scripts data to give us more information about outpatient
14 use, and then we have two contracts with two
15 organizations, CCS Associates and Metaworks, both of whom
16 are here today. We will try to meet with them and talk
17 with them.

18 These will do professional, scientific-level,
19 publishable literature assessments, systematic literature
20 reviews, and meta-analyses wherever possible.

21 So I'm going to list a bunch of questions, and
22 then I'm going to sit down. People are free to bring up

1 additional questions or to, even better, try to answer
2 these questions, because I think we know many of the
3 weaknesses but we don't have the answers. So help us by
4 showing us our weaknesses, but also help us by coming up
5 with some solutions.

6 There are many criteria to be considered, and
7 we are all aware we need to think about severity, we need
8 to think about racial/ethnic disparities and differences,
9 therapeutic index, availability of alternative therapies,
10 and here I am talking about operationalizing these
11 criteria in a way that can be measured so that people
12 don't just weigh it in an intuitive sense but we can rank
13 things and quantify things.

14 I think with severity we are going to use some
15 of these measures: mortality, hospitalization, physician
16 visits, chronic conditions, and limitations on growth,
17 independence, and development. Those will be some of our
18 measures of severity.

19 We are doing this analysis with AHRQ, and I
20 just wanted to put before you the top 10 diagnoses
21 associated with hospitalizations in this era, the 17-
22 year-old age group. This is from 2000. We have an

1 extensive analysis here that will be coming out. We have
2 broken this down by age groups and by race and sex, as
3 well as payer status.

4 It is clear, for example, we have these three
5 respiratory conditions: pneumonia, asthma, bronchitis.
6 We have epilepsy as a discharge diagnosis across all age
7 groups, and we have affective disorders up there. So
8 these are some very critical issues in pediatrics, and
9 they help us know what diseases we need to have an impact
10 on in addition to the others. When you break this down
11 by age group, of course, there are different diagnoses.

12 BPCA does address racial/ethnic differences,
13 and as I understood it, originally this was interpreted
14 as genetic variation in response to drugs. We know that
15 there is variation in the occurrence of indications or
16 conditions as well as variations in our ability or
17 success in diagnosing conditions, and additionally
18 variations in treatments of conditions, which translates
19 into frequencies with which drugs are given to different
20 racial/ethnic groups.

21 I think as a byproduct of the work we are
22 already doing, without additional cost we are going to be

1 producing some very interesting data in this area.

2 This follows exactly what Dr. Zito presented
3 about drug use, but these are hospitalizations for
4 affective disorders by race/ethnicity per 100,000. You
5 see the number is much higher in whites, lower in blacks,
6 lower in Hispanics, lower in Asians.

7 We don't know if this is because of a
8 difference in the underlying incidence of disease or
9 differences in diagnosis, or I don't know if this is a
10 success in treatment or a failure in treatment, to tell
11 you the truth. So there is a lot we don't know.

12 The same here for the patterns for pneumonia,
13 bronchitis, asthma, these three top respiratory
14 diagnoses. Patterns are very different. We know about
15 the increase in asthma in blacks, but it looks like
16 Hispanics have a different pattern, with the highest
17 levels of pneumonia and bronchitis being in the Hispanic
18 population. Lower levels, it seems, of everything in the
19 Asian population. So there is much to be looked at here.

20 This is going to be one of my pet projects
21 because I fell across this, and as an epidemiologist, I
22 thought this was very interesting. Why would one

1 racial/ethnic group be more likely to be hospitalized for
2 burns. Actually, there are a whole bunch of good reasons
3 related to cost of housing, the age of the mother,
4 whether the mother is a smoker, and urban/rural living.
5 It actually fits together so that we see that black
6 children are at higher risk of being in the hospital
7 because of burns and thus in a group that would be
8 treated with all the different treatments related to
9 burns.

10 Shifting now, one issue we have with BPCA is to
11 coordinate the process that takes place here with the
12 Oncology Subcommittee. We know we have to do it. We
13 haven't figured out how to do it, so it is on our to do
14 list for this coming year.

15 We want to continue expanding our contact with
16 different medical specialties. I think this year we
17 brought in Dermatology, and I hope we stay in touch with
18 Dermatology. I don't know how many other groups we need
19 to bring in. We may need a dentist, and there are other
20 groups that we might want to think about.

21 I guess I'm taking advantage of having the
22 microphone. This is one of my little issues.

1 It seems when we study these off-patent drugs
2 that because they are older drugs, some of our concerns
3 are more on the safety side than the efficacy side. What
4 this is doing to us is driving up our sample size
5 requirements by an order of 10 at least, which translates
6 into cost and decreases the number of drugs that we can
7 study.

8 As an epidemiologist, I really think the
9 appropriate way to study safety endpoints is through
10 observational studies rather than through randomized
11 clinical trials. I think it is at least an alternative
12 we have to review and consider. It is very compelling
13 because the safety issues are so dominant in so many of
14 our discussions.

15 It is also interesting, and I think we were
16 talking earlier, some of us, about the difference between
17 thinking about a disease and following from disease to
18 drugs rather than following each drug individually. The
19 dermatologics is a good example. They are used
20 interchangeably and in combination with each other. It
21 makes sense to me.

22 I can see the kind of massive study that would

1 just cover all the dermatologic drugs at once, but we
2 could also have a similar kind of study that looks at the
3 whole scabies/lice question and all the treatments at
4 once and sort of gets the whole issue taken care of. We
5 do have to break them down because of the written
6 requests, but it would be nice to be able to coordinate
7 these issues to some degree.

8 Then, opening it up for other issues and
9 comments. I'm going to go sit down and now I'm turning
10 it over to all of you.

11 **Comments and Discussion of the Process**

12 **Dr. Robert M. Ward, Moderator**

13 DR. WARD: Let me ask people to start with the
14 comment on information provided to you and requested from
15 you. Are there some specific, concrete areas where we
16 could have improved that?

17 DR. BERQUIST: I thought that it is helpful for
18 us to know more specifically why we were reviewing a
19 particular drug. What I found was helpful was this book
20 here, where you have the requests. I know that might
21 introduce some bias in and of itself, but I still think
22 it helps us to sort of focus. I would encourage more

1 specificity about why you are choosing a particular drug.

2 DR. WARD: Bill?

3 DR. RODRIQUEZ: I have a bias, and you are
4 going to hate me for it, but I think each one of you
5 should give us some information, because you all had your
6 own personal experience on the subject. Believe it or
7 not, everything that you went through is valuable to us,
8 so don't minimize it. So share with us your thoughts:
9 what would be the ideal; what would be the dream process
10 for you in terms of information. We want to hear from
11 everybody.

12 DR. WARD: The thing that struck me as I was
13 going down this list and looking at the final ballot as
14 it comes out is that there are specific age ranges that
15 frequently impact our decision-making. Those could have
16 been listed. We could have known that.

17 For the FDA people who are, maybe, out there
18 also, I would ask that the FDA folks be here for both
19 days, the whole group. There is a lot to be added. You
20 have a vast experience in pediatrics and therapeutics to
21 share with us as well, and I think it helps the process.

22 Steve.

1 DR. LAWLESS: Yes, two things. One is just a
2 general comment and the other is thinking out of the box.

3 The general comment actually is, it would have
4 helped a little bit when doing the evaluation to have
5 almost like a tradeoff analysis. Everybody can be very
6 passionate about their different specialties, and so
7 whoever can mix with the rheumatologists or neurologists
8 or dermatologists or intensivists and how convincing
9 their argument is.

10 So a tradeoff so people put it in that
11 perspective would be kind of a nice way in terms of their
12 evaluation.

13 Thinking out of the box actually is, a lot of
14 us have actually gone to an electronic medical record.
15 So the backbone of a lot of this that is going on can be
16 written as specifications in any electronic medical
17 record.

18 So if you are putting in things like what is
19 the indication, why are you using this drug, and linking
20 it and having the programmers actually behind the scenes
21 link it to some of the other side effects and that kind
22 of stuff. There are a lot of us doing national efforts

1 on this kind of stuff, but thinking out of the box, a lot
2 of what you are doing in terms of the meta-analysis could
3 be done with a query of a database, and that could save a
4 lot more time and effort, rather than having to back and
5 reinvent the wheel.

6 DR. WARD: Can you convince your medical staff
7 to do that?

8 DR. LAWLESS: Yes, actually, we are.

9 DR. WARD: Okay. I have heard of others that
10 are doing that, and if you can, you are absolutely right.
11 We actually have a database that has every dose
12 administered in our children's hospital per year. You
13 just have to go query the right population.

14 DR. LAWLESS: Absolutely. The thinking-out-of-
15 the-box part of it in terms of putting people to do that
16 would make it so much easier. Then you will see where
17 the off-label things are coming from and you will see the
18 side effects. It really is at the fingertips.

19 DR. WARD: Yes.

20 DR. ZITO: Just a few comments.

21 DR. WARD: Go ahead.

22 DR. ZITO: Steve, I'm not really clear. I

1 think it is not as simple as you are presenting, or at
2 least I'm not sure where you are going with that. What
3 goes on in Hospital A could be very much a regional
4 issue.

5 So I don't know whether you were suggesting
6 that frequency of information would be provided to that?

7 DR. LAWLESS: No. Actually, the key word,
8 which you hear more about in electronic medical records,
9 which is actually the thing that is making them
10 difficult, is the word "integration" of them. If you
11 have your pharmacy system that integrates with your order
12 entry system which integrates with your laboratory
13 system, they all get linked nicely.

14 What drives up the expense for most people is
15 creating those interlinkings, because you have the best
16 system here, the best system there, but with a little bit
17 of writing of specs and the interfaces, you actually can
18 have labs interfere with the order entry which interfaces
19 with some of the other electronics.

20 When you do all that together, then you are
21 almost having a system of pharmacokinetics and
22 pharmacodynamics being set up.

1 DR. ZITO: So if I hear it, then you are
2 pushing an agenda in which we could evolve really good
3 community-based treatment information through this
4 contract process. Is that what you are saying?

5 DR. LAWLESS: Yes.

6 DR. ZITO: Great.

7 DR. LAWLESS: Actually, the different parts of
8 the FDA and the CDC are actually working with the HL7
9 groups to do something along these very similar lines to
10 create those languages.

11 If you do it with a mind set of saying, how are
12 we going to do it for this, with the forethought of doing
13 it because pediatrics is very specific, you can actually
14 start getting these things: how the CDC is changing, if
15 you change this drug versus something. You have the
16 numbers, which you don't have normally. So you are
17 dealing with millions of records at a time rather than a
18 couple of hundred.

19 DR. WARD: And they have diagnosis-related
20 prescribing.

21 DR. ZITO: I have a couple of quick comments in
22 relation to Dr. Lasky's comments about the dimensions

1 that you are interested in us for reacting to and the
2 difficulties we all experienced together in trying to
3 fill out the rating form. So probably, the rating form
4 is something that you are going to be looking at.

5 I wondered as I went through it, I guess the
6 problem is that it is really organized a lot about what
7 the FDA needs in order to add to the labeling. Maybe
8 that is not the problem, that is the mission. I
9 shouldn't be saying it in a negative way.

10 But for some of us, as Dr. Lawless just
11 expressed, traditionally there have been dimensions that
12 have been radically missing from the information that is
13 given to the clinician. We have tried to fix that in
14 sort of small fix-it, band-aid ways.

15 For example, you might see an epidemiologic
16 statement that says, well, the occurrence of neuroleptic
17 malignant syndrome in this drug is one in 65 billion. So
18 that invites the clinician to turn around and say, it is
19 not me, it is not important.

20 So there have to be fixes that go beyond that.

21 So in our ratings, maybe we could come up with a way of
22 assessing the impact on quality or the need for better

1 quality assurance on this drug, or if we add this
2 information to the label, what is the public health
3 impact, maybe something like that.

4 The second point is, best practices which go on
5 very well in the academic centers and never get
6 promulgated to very many of the people that are out there
7 that are too busy or not being paid to perform best
8 practices as opposed to usual practice, which I think
9 needs to be a driver here. In other words, if it is
10 being widely used, we need to make some assurances that
11 the labeling additions would either lead to abandoning it
12 or the other way.

13 The third point is comparative trials. It
14 seemed like we could fix a lot of the problems in the
15 drugs on the list by setting them up as comparative
16 trials, which is much more important in the public sector
17 because traditional trials against placebo response are
18 necessary but not sufficient to make a decision for us to
19 use the drug and to use it in a cost-effective way.

20 The final point is long-term use. I would beg
21 that the trials that do get conducted not stop at four
22 weeks. For any drug that needs to be chronically used,

1 at least some one-year outcomes should be urged.

2 DR. WARD: Alan.

3 DR. STILES: This is sort of a mom and apple
4 pie comment. Excuse me for making it.

5 First, I have to react to the best practices in
6 academic centers. You are absolutely wrong about that.
7 Each academic center is each academic center, and each
8 practitioner, unfortunately, by and large functions as an
9 individual without knowing what their benchmarking is and
10 without actually doing best practices. Although to ask
11 them, they will tell you they are doing best practice.
12 So that, I think, is a really big issue, and something we
13 have to address.

14 I would suggest we add somewhere on the
15 evaluation sheet something to measure the view of the
16 reviewers as to clinical relevance of the drug that we
17 are deciding to look at. It even started coming out in
18 the discussion one way or the other, but often being able
19 to get that particular point across may make a difference
20 in how it ends up on the priority list.

21 DR. MEYTHALER: I would also like to favor
22 adding in what he is saying on the relevance. Having

1 almost a tiered number, like a five or six, a set number
2 of this is an orphan drug, and then population numbers,
3 and literally a check-off of the number of incidents and
4 then prevalence and then mortality issues, those three
5 categories. Maybe you have a five-level tier issue with
6 population.

7 You need to put your money where you are going
8 to have the biggest effect.

9 DR. MATHIS: Just to piggyback on this, the
10 BPCA was indeed passed to fill gaps in labeling for drug
11 products. That is why we look at the gaps in the current
12 labeling, because that is what our congressional mandate
13 is.

14 When we are trying to decide for on-patent
15 drugs, which is under the BPCA process, one of the things
16 that we try to do to assess whether or not we should
17 issue a written request is to determine the public health
18 benefit. We go through this process every time we are
19 writing a written request. One of the ways that we
20 determine that is the number of patients affected.

21 Previously, under FEDAMA, we looked at 50,000
22 as the number of patients that we thought was

1 significant. Although that is not written under BPCA, it
2 is still kind of the number that we use, but then we
3 balance that against, is this going to be a significant
4 improvement in treatment for even a small number of
5 patients.

6 So either a significant number of patients or a
7 significant impact even on a few patients would make a
8 public health benefit.

9 We also balance that against current
10 alternatives. If we have newer, safer drugs that are
11 much better than the older drugs, we are not going to
12 issue a written request for the older drug because it is
13 yesterday's story. It is not what we want to use in
14 practice any longer.

15 Then, the third point about what we get into
16 the labeling as far as education goes, I do think that we
17 need to be very careful with that, because as you know,
18 the FDA does not regulate the practice of medicine, and
19 we don't want to start doing that. We want to give
20 physicians a little bit of freedom to use their judgment
21 when they are treating patients. However, we could all
22 join together in a broader effort to educate physicians

1 about drug use.

2 DR. WARD: I think some of the more recent
3 labels listing frequencies of various adverse effects and
4 real incidence, number affected divided by number
5 prescribed, are so useful. I really found the
6 dermatologic products a fascinating discussion because
7 they are widely used in children by lots of different
8 prescribers. The more definite information that we can
9 provide them about effectiveness and toxicity, the better
10 kids will be treated.

11 Yes, Bernie.

12 DR. WIEDERMAN: Just a couple things. One, to
13 re-echo in terms of the scoring system, when I look back,
14 and I think I remarked yesterday, my point totals almost
15 were the reverse of what I felt was important. I think
16 it had to do with the fact that, are there alternative
17 therapies available; or where does this drug fit in the
18 vast scheme of things. It got lost because everything is
19 assigned an equal value on that score sheet. So to sort
20 of lend support to the combination of your scale of
21 things.

22 The other thing is what to do with those

1 comments and input. I think it would be helpful to the
2 reviewers to get that information along with everything
3 else that is said, but to have some kind of vetting
4 process so that if someone wants to study Cefuroxime in
5 under three-month-old sickle cell disease patients and
6 somebody says, "Wait, I'm not sure I understand that,"
7 and they are literally calling the person and asking,
8 "What did you mean by this?"

9 I still worry that we are missing something
10 that was important and we just didn't get it. So it is
11 tough.

12 Then, just one comment for Tami. I noticed on
13 your Top 10 Diagnosis List acute bronchitis, which I
14 think most of us would say there is reasonable discussion
15 that it is a diagnosis that doesn't exist in pediatrics.

16 I don't know what that is representing, but it is not
17 acute bronchitis hospitalization. There is coding for
18 bronchiolitis, so maybe that is it, but before you get
19 sold on that, make sure what it really is.

20 DR. LASKY: I see a whole Ph.D. dissertation
21 for someone who wants to look at the patterns of
22 assigning the different respiratory diagnoses and which

1 ones appear with which other ones in what order. It is
2 really a complex issue, and it is definitely inadequate
3 in many ways, but this is a database that is a
4 probability-based sample of the United States and so has
5 the advantage of being standardized, if not adequate from
6 the other points of view.

7 DR. ZITO: A question on that. Are they ICD
8 9s, then?

9 DR. WARD: But in each hospital, a coder in
10 medical records frequently is the one assigning that code
11 looking at the chart.

12 DR. RODRIQUEZ: Could I say something? One
13 thing that we have dealt with before with this is
14 specifically finding out what is actually included under
15 bronchitis. That information should be available because
16 it should give us the bronchiolitis, it would give you
17 acute viral respiratory infection, low respiratory
18 infection, and they are all lumped together.

19 But I agree that bronchitis is not a pediatric
20 diagnosis.

21 DR. LASKY: Just returning to this, what we are
22 going to do is use the database as it is and basically

1 produce a listing. People need to comment on it and go
2 to AHRQ and ask them about any of the data definitions,
3 because they are published. They have come up with this
4 clinical classification system which groups together
5 related ICD 9s, so you have 259 categories instead of all
6 the ICD 9s.

7 In some cases what they have done is changed
8 the name of the illness to a kind of vernacular.

9 DR. WARD: It may be bronchiolitis.

10 DR. LASKY: I think, on one hand, it needs in-
11 depth exploration, but I don't think we are going to be
12 able to do it.

13 DR. WINER: Tami, is this the kid database?

14 DR. LASKY: Yes.

15 DR. WARD: Yes, Dr. Epps.

16 DR. EPPS: First of all, I just wanted to thank
17 Dr. Mattison and Dr. Mathis and Dr. Lasky and Dr. Ward
18 for a very smooth meeting, as well as the staffs of the
19 FDA and NICHD. It was a very interesting meeting.

20 Basically, I guess one thing that I feel just
21 generally is, I think information is powerful. I think
22 when I'm trying to decide, I usually err on the side of

1 more information. I think the more information that
2 practitioners have, the more information patients have,
3 the better.

4 When I participated in one of the advisory
5 committees, sometimes the feeling was that, well, let's
6 approve the drug and get the post-marketing data. We see
7 how that goes with Vioxx, okay. It doesn't always go
8 very well.

9 DR. WARD: Got it.

10 [Laughter.]

11 DR. EPPS: Certainly, I mean, we found it
12 quicker, sooner than later, in that regard. Certainly,
13 dermatology is not like pneumonia, where you have a nice
14 X-ray. Everyone can't even agree on the diagnosis all
15 the time. I mean, they are still trying to define atopic
16 dermatitis, the North American group versus the
17 Europeans, and on and on.

18 So sometimes we have those problems, which is
19 why sometimes it is very difficult when we are assessing
20 dermatology studies and deciding, well, did that person
21 really have eczema anyway when they were testing it.

22 To put on my pediatric hat, I think

1 pediatricians mean well. I think they try to do what is
2 right for their patients whether they are at an
3 institution or in private practice. Parents are very
4 savvy. They are on the Internet. You have to keep up.
5 They are reading the same studies you are, and some other
6 stuff that is probably floating around in cyberspace.

7 DR. WARD: That is not a study.

8 DR. EPPS: Correct, that is not a study, but
9 because it is typed out and in writing, it could be true
10 from their perspective. So I think everyone is trying to
11 pay the best attention.

12 As far as data that we may need, certainly,
13 like age of onset, whether it is acute or chronic,
14 prevalence, certainly mortality is important, but
15 morbidity is extremely important. I mean, a lot of
16 conditions that we have talked about cause chronic
17 disease, a lot of illness, may impact the whole family,
18 days lost from work and school. They are very expensive
19 if not treated properly.

20 Perhaps we can get some data from N. Hanes, I
21 don't know. We have been fighting to get acne put on
22 there. They don't think it is important, but just

1 prevalence of some common diseases may be there. Without
2 going through the Kaiser or the whatever, I don't whether
3 we are up to four by now for N. Hanes or if it is in
4 process. Who knows. Anyway, that may be a source. I
5 know N. Hanes-3 is out there.

6 I agree with whether it is clinically relevant.

7 I think that is very important. That would be paired
8 with incidence as well.

9 Back to the dermatologic issues, unfortunately,
10 we do have some tools that people have tried to use.
11 Some of them are SCORAD and some others which are
12 controversial, but there are efforts being made to try to
13 uniformly assess some of the dermatologic conditions if
14 you decide to go that road.

15 I do think one of the more important things is
16 certainly the public health benefit and trying to find
17 the best result for society in general.

18 DR. WARD: One of the things that has come up
19 in discussions about neonatal outcomes is long-term
20 follow-up. One of the challenges in pediatrics is
21 sorting out the effects of the various disease processes
22 from the effects of the drug long-term. I think that

1 will always remain a challenge for us.

2 DR. STILES: Plus, we have changing therapies
3 that affect outcomes between the times you are trying to
4 look at the question. So we remain several years behind.

5 DR. PURSLEY: Plus, we have the issue of
6 socioeconomic overriding all of those medical and
7 conditional effects.

8 DR. WARD: Not that it is difficult to do.

9 My final slide in the talk about perinatal
10 substance abuse is that if you did not assess the
11 underlying socioeconomic condition the child was reared
12 in, you miss the predominant effect. So we can attribute
13 it to any number of drugs or complications if we create a
14 superficial analysis.

15 Yes, Dr. Sachs.

16 DR. SACHS: I was actually kind of curious
17 about you all's opinion a little bit of the input process
18 from the experts. One of the other things that I'm
19 privileged, I will say, to do is serve on the Academy of
20 Pediatrics Committee on Drugs.

21 As you guys may know, the Committee on Drugs,
22 for example, issues statements periodically about certain

1 things, and right now there is a statement that is in the
2 works on emergency drugs that all pediatricians should
3 have in the office, for example. That has a list of
4 many, many, many drugs, some of which -- I will daresay
5 most of which -- are not labeled in kids.

6 That is a very pragmatic source right now of
7 drugs that are being recommended by, presumably, an
8 expert group for everyone to use. It just kind of occurs
9 to me that there may be similar things that you all as
10 experts are aware of that we may not be that would kind
11 of be useful, especially if we are not hearing from that
12 group.

13 If we didn't hear from the American Heart
14 Association, I mean -- this time we did, but let's say we
15 really wanted to look at SBE prophylaxis. It would be
16 silly not to look at their recommendations, and I think
17 we would consider that.

18 But just as a starting source, instead of an
19 individual nomination, if you have this statement, I was
20 just curious what you guys thought about that type of
21 input.

22 DR. WARD: Steve.

1 DR. LAWLESS: If you look at risk management
2 data and liability data, I'm not an advocate for creating
3 more work for lawyers, but if you look at what has gone
4 on in risk management, what have those drugs actually
5 been associated with: product liability with risk. If
6 you use that as a guide, you can actually see sometimes a
7 little bit more of a different slant on things.

8 A lot of it may not be the drug itself. It may
9 be what you are talking about.

10 The use of Epinephrine. In the use of
11 Epinephrine, the indications for the drug are proper.
12 However, the mechanism of how it is delivered may be
13 improper. So you have calculations of how difficult it
14 is to do calculations of Epinephrine. So you may find
15 some surprising ways of looking at that, which is
16 implying what you are talking about the emergency drugs,
17 for example.

18 To do an Epinephrine infusion takes four or
19 five people to take their calculators out to do it, and
20 side effects follow.

21 DR. WARD: Yes.

22 DR. SACHS: Actually, I just wanted to say

1 something that I found very powerful and helpful. I
2 mean, several of the drugs that came up on superficial
3 glance, I can say that I looked at them and said, "Well,
4 gosh, there is adequate information in the label. It is
5 labeled all the way down to this age or that age," not
6 necessarily understanding that in practice the duration
7 of treatment is different, or the dose that is being
8 recommended is outdated.

9 I think that is information that has been very,
10 very powerful. I am not 100 percent sure that we would
11 get that feedback otherwise.

12 I mean, I just, for one, want to thank everyone
13 for the very good quality of the presentations. I mean,
14 I guess you guys aren't called experts for nothing.

15 [Laughter.]

16 DR. ZAOUTIS: Two comments; one small one
17 regarding the scoring system. One of the things I heard
18 from people was regarding the safety of the drug for this
19 indication versus the safety of the drug in general. I
20 think for safety specifically, the drug has been used in
21 X-number of patients and studies of the safety may be
22 less of an issue to break out by indication, or have an

1 additional score for general safety across all
2 indications. For efficacy, it is much more important for
3 that indication.

4 The other is, there are threads of this, and
5 Tami got up there and mentioned this. Although the
6 mission, from what I understand, was to look at these
7 drugs, I think it provides an opportunity to study
8 diseases in children where we do not know how to manage
9 them appropriately.

10 It was obvious in the discussion about
11 influenza and thinking about the design of a study
12 comparing Amantadine and Rimantadine. Now, those were
13 the drugs that were the triggers here, but there were
14 other drug options. This may be the time that we can
15 address bigger questions about diseases and what is the
16 best way to manage a disease.

17 The same thing was obvious in the finding about
18 the over-the-counter Hydrocortisone, how that has not
19 been studied long-term in the treatment of eczema.

20 So I think a conceptual framework that starts
21 with the disease should be considered.

22 DR. WARD: Would you respond?

1 This seems to be one of the real conflicts
2 having to do with labeling. We begin with a drug and
3 then what its indication is, as opposed to starting with
4 an indication and let's talk about all the drugs.

5 DR. MATHIS: Right. I actually think that that
6 is a very good approach because one of the other things
7 it does is it helps us address the needs in the pediatric
8 treating community if we start with the indication.

9 The other thing is, too, that frequently, like
10 you said, drugs are used off-label. We saw that with
11 Amantadine. There might be bigger uses for a drug other
12 than the current labeling.

13 Now, frequently we know that and we can give
14 that feedback. When we talked about Clonidine, we
15 certainly didn't talk about it for hypertension because
16 we knew it was being used off-label for TIC disorders and
17 ADHD.

18 However, approaching this process by looking at
19 most frequent diseases or diseases that are in most need
20 of therapies would allow us, I think, to survey the users
21 much more efficiently. What drugs are you using for this
22 indication at this time that you don't think have

1 labeling for it.

2 DR. ZAOUTIS: You will eventually get to the
3 data about the specific drugs.

4 DR. MATHIS: That's right, that's right.

5 Just to take the opportunity to comment about
6 safety in relation to the indication, you're right,
7 frequently we can say this drug has been used at this
8 dose for another indication so we know the safety
9 profile. Frequently, as we are looking at approving a
10 drug, we have to look at the risks in light of the
11 benefits, which is the difference between if you are
12 treating cancer versus acne -- excuse me, Dr. Epps.

13 I mean, there certainly is, really, a different
14 benefit profile that you have to weigh the risk profile
15 against.

16 So I think that is probably where that came
17 from, but you're right, frequently we can look at the
18 risk profile from another indication where the dosage is
19 the same.

20 DR. ZAOUTIS: I'm just saying, maybe in
21 reviewing, adding a score for a lot of data in another
22 indication.

1 DR. MATHIS: Yes, definitely.

2 DR. MATTISON: Just a follow-up, you heard Tami
3 describe her interest in collecting data on conditions.
4 The fact that Congress put together the NIH and the FDA
5 suggests that they intended to improve the label
6 information that is available to practitioners caring for
7 patients, but they also understand that the NIH has a
8 different mandate from the FDA. So we have looked at
9 that as an opportunity to think critically about
10 conditions that occur in pediatric populations.

11 The comments, for example, about why are kids
12 admitted to hospitals with burns, I think, points out
13 some of the kinds of information that we are going to
14 sort of begin to probe and ask questions that are sort of
15 outside of our own venues a little bit.

16 DR. WARD: I think that is excellent.

17 One other point I would make, though, is that
18 with respect to the safety, in specific patient
19 populations and disorders, the safety margin and the
20 effects may vary. There may be more adverse effects that
21 show up in a particular disorder.

22 So I would be careful with that extrapolation.

1 It is complex.

2 Debi.

3 DR. AVANT: I think it is a great idea to start
4 with the indication, but we also need to remember the
5 patent status of the drugs.

6 PARTICIPANT: We have been caught on that,
7 haven't we?

8 [Laughter.]

9 DR. LASKY: We will try.

10 PARTICIPANT: There is nothing to say we
11 couldn't look at the indications, list the drugs that we
12 need studied, and then screen out those that are still
13 on-patent.

14 DR. LASKY: Debi, you have to not let these
15 off-patent drugs go on-patent again.

16 DR. AVANT: I'm going to work on it.

17 [Laughter.]

18 DR. WARD: Again, this may be why this
19 comparative process that we have talked about may be
20 helpful so we could take the off-patent and on-patent and
21 do some comparison studies.

22 DR. LAWLESS: Just out of curiosity, is there a

1 listing for each of the drugs, an electronic list, and
2 the different organizations that actually say, these are
3 the on-label uses? We can't have a listing of off-label
4 uses, but on-label uses of these drugs?

5 DR. WARD: No.

6 [Laughter.]

7 DR. WARD: I asked for that in '97. I said,
8 "Where is your database about labeling?" Each division
9 keeps it, and each in a different database.

10 They have made some progress toward reconciling
11 those variations. The newer things, I think, are being
12 entered into a common database.

13 DR. SACHS: There is a "Drugs at FDA" website
14 now. Just go to the FDA link. I think it is "Drugs At
15 FDA." You just punch that in. If there is a current
16 label available, it is available.

17 The problem is, with some of these old drugs
18 that are off-patent and there are a lot of generics, the
19 labels are a little harder to come by, but that is
20 something we are actively working on.

21 DR. LAWLESS: Because if you are talking about
22 the electronic part of it and you have that, that is the

1 thing that links it. Are you using it for these on-label
2 things? No, I'm using it for something else. It would
3 help that way.

4 DR. LASKY: Yes. We have been wishing for a
5 while.

6 DR. WARD: John.

7 DR. ALEXANDER: Just a couple of things. I
8 mean, realizing that we are talking about drugs that are
9 now off-patent, I think that one of the things that we
10 need to think about is exactly how and what process are
11 we going to be using to sort of decide on whether
12 something needs to be studied or not.

13 Under the law, when FDA is looking at those
14 drugs that are new that are just released and are on-
15 patent, we sort of have to assess those drugs, and it is
16 fairly easy because the only things that those drugs have
17 really been studied or proven for are actually the
18 indications that they are seeking for those new drugs.

19 So it is easy for us to sort of go into the
20 process and just say, okay, so which of these diseases
21 that we are dealing with are important for pediatric
22 patients; which ones do we need information on younger

1 age groups, down to how young; and whether we can
2 actually extrapolate information from adults down to
3 pediatrics.

4 With this process, the off-patent process, part
5 of the difficulty is that we are dealing with drugs that
6 have been out there for ages, and in some cases where we
7 are sort of looking at drugs that practitioners feel they
8 have adequate information on and are using it already, or
9 in some cases, they don't have adequate information on it
10 and are using it anyway.

11 So that is sort of what makes it difficult to
12 try and assess this by the same sort of disease-based
13 process. A lot of times there are new drugs that have
14 come along that are still on-patent, and those are the
15 ones that we really ought to be referring to, like the
16 discussion that we had earlier on, Cyclosporine versus
17 Tacrolimus and Sarolimus and the others.

18 Then, in other cases, the thing that is really
19 generating something ending up being on the list is
20 specific safety questions that come out for a particular
21 drug. Those studies are usually hard to do because, if
22 it was a common safety problem, you wouldn't be using the

1 drug. It is usually an uncommon safety problem, the
2 example being Erythromycin and pyloric stenosis, that are
3 then difficult to go in and do studies on unless you are
4 talking about large trials.

5 DR. ZITO: I just want to say, we don't have to
6 only talk about large trials. That is our bias in the
7 United States, there is no question about it, but the
8 safety research could be addressed from different
9 designs, particularly for a drug that has already been
10 out there for 50 years. You would have more confidence
11 then that the unique things or the big flag things would
12 have shown up through MedWatch. So now you are really
13 going for more nuanced understanding of chronic exposure.

14 For example, we studied Pemoline as an example
15 of a safety issue. Pemoline was out there as a treatment
16 for ADHD. It came to the United States somewhere in the
17 '80s for the elderly for wake-up-your-brain stuff. It
18 didn't work very well for them, so they said, well, let's
19 try it in the kiddies.

20 You need more than one drug in a class, so
21 people adopted it. It was never really a big world-
22 beater, but it was there as an alternative.

1 It has taken 26 years to discover that it
2 produces liver transplants or death in children. So the
3 hepatotoxicity is a real thing. I mean, I don't know if
4 you want to randomize kids to a trial to convince
5 yourself of that, but it is off the market in Canada, it
6 is off the market in the U.K., but we don't take it off
7 the market in the United States because we don't want to
8 deprive the handful of people that are left out there
9 that are in treatment.

10 So we really have some problems about attitude
11 around safety stuff. I think this is a great opportunity
12 with the off-label to think about some creative ideas for
13 answering that question about safety.

14 DR. ALEXANDER: Understood, but at the same
15 time, I think that Erythromycin points out an example of
16 where that sort of system and that sort of looking at
17 drugs from what we are stuck with, which in the past has
18 mostly been a passive reporting system, didn't really
19 give us the answer 50 years into its use.

20 DR. ZITO: So something between MedWatch,
21 ideally.

22 DR. LASKY: I was going to say, in between

1 passive reporting and randomized clinical trials. There
2 are a whole range of study designs. Some of the best for
3 adverse events are the case control studies, but there
4 are other study designs as well that can be used to
5 collect very convincing data and sound scientific data to
6 test a hypothesis of the relationship between a drug
7 exposure and an adverse event.

8 So we don't have to go from one extreme to the
9 other. We can find the middle ground.

10 Something else to throw out which I hadn't put
11 on the slides, but people have approached me with data
12 from Europe, particularly from England. I think at CHOP
13 you have the British --

14 DR. WIEDERMAN: The GPRD database.

15 DR. LASKY: Right. I think we need experts to
16 help us understand when we can use European or Asian data
17 and when we can't use it. What are the limits. We don't
18 have to redo everything, and some things are done in
19 Europe or in Asia, but some things do have to be done in
20 the United States. So that input would be very valuable.

21 DR. WARD: The Erythromycin experience, I
22 think, is actually instructive. I find lots of

1 historical things of constructive value.

2 There was the signal that came out in the six
3 cases in the Carolinas that Peggy Honine [ph] reported.
4 It has been confirmed by going back to the Tennessee
5 Medicaid database and looking at exposure to Erythromycin
6 and then the diagnosis of pyloric stenosis.

7 So we have done both, but you have to have that
8 signal. Nobody went to the Tennessee database and found
9 this at the beginning, so we need the astute clinicians.
10 We need the observers.

11 DR. ZITO: I would suggest, when you have one
12 Medicaid Tennessee database and you are looking at a drug
13 like Erythromycin, you are in better shape than when you
14 are looking at a much smaller exposure.

15 We have 50 states of Medicaid with that
16 capacity that sits at CMS every year where, if we were
17 funding a research initiative that would look for those
18 small exposures, we could examine some questions on a
19 regular basis.

20 DR. WARD: We had the transplant population
21 where they receive a minimum of five or six drugs a day
22 and we try to sort something out.

1 DR. ZITO: That is very tough.

2 DR. WARD: That is the complexity.

3 DR. STILES: There are two other things you
4 probably ought to consider, and I sort of shudder to
5 bring both up.

6 One has to do with cost, because clearly, we
7 have some medications out there that are astronomically
8 expensive and are being used not as labeled and really
9 push the cost of care, particularly where we have such a
10 large group of children with chronic disease that fall in
11 the Medicaid population.

12 So I don't know how to factor that in. I do
13 know that there are a number of those there that we
14 struggle with every year in our state when we try and
15 figure out how to set up the listing of what we are going
16 to pay for and not pay for.

17 The second thing is that because all hospitals
18 are being driven toward outcomes reporting, we will have
19 an opportunity to see where there are things that have
20 wide variation and outcome to help us consider whether
21 there are things we ought to be looking at within that.

22 Now, I have no clue how to approach that. I'm

1 just bringing it up as an issue, but places where there
2 are variability are likely also to be places where we are
3 going to find issues that relate back to these
4 medications.

5 DR. WARD: I think you are probably very right.
6 The more complex the disorder, it seems the greater the
7 number of medications undertaken or used.

8 DR. MATHIS: I would like to somewhat reassure
9 the group that the FDA is working on more active
10 surveillance of adverse events. We are trying to figure
11 out the best way to do that.

12 Dr. Solomon Iyasu, who was here earlier -- he
13 is not here now -- is with the Division of Pediatric Drug
14 Development. Of course, as always, pedes is in the
15 forefront of trying to pull together a lot of safety, but
16 he has been working very closely with many of the review
17 divisions as well as with the Office of Drug Safety to
18 try and figure out where that middle surveillance program
19 is. That way, it is not completely passive.

20 Obviously, we can't do a completely active one
21 without violating everybody's privacy. However, there is
22 something in between, and he has really been working on

1 that hard. We do see that as a very important issue that
2 the FDA needs to address.

3 DR. WARD: Yes.

4 DR. GRAYLOR: A few comments related to a
5 couple things that were just said.

6 Tami, first, in your bullets about getting
7 better data from the European and Asian countries, there
8 have been a lot of efforts and coordination of some
9 activities related to large databases in Europe and Asia.
10 We have had some frequent recent discussions about them,
11 and perhaps we could explore to see if they made sense
12 for you later.

13 One of the other issues that you just talked
14 about was basically related to FDA's activities in some
15 of the broader areas. It relates also to some of the
16 activities related to the electronic medical record
17 before.

18 Back when I was at the FDA, we were very much
19 involved with some of these standards activities and
20 seeing how the agency could be more actively involved in
21 the standards community so that we could have better
22 access to the information and use it more effectively.

1 When I retired from the FDA, Randy Levin took
2 over my role in the HHS Data Council, and he has been the
3 one who really was active from the early days in terms of
4 the FDA interaction with HL7. So I think he would be a
5 good person to talk to.

6 To look further to the future, David Raylor
7 [ph], who is the Health Information Technology lead for
8 the department now, is very much interested in
9 pharmaceutical issues. I talked with him a few weeks ago
10 at a meeting we were both at, and I think in terms of
11 development of the future infrastructure and one of the
12 key issues we talked about really is the really rotten
13 infrastructure we have to many extents. Well, let's say
14 it is not perfect.

15 I think there are some opportunities in giving
16 him some opportunity to really think through providing
17 input on some real applications that he would find very
18 interesting to build into what the department will
19 support in the future as a real possibility.

20 The last thing I will mention is in terms of
21 the best practices issues we have talked about. Clearly,
22 in terms of having an impact sometimes, another group I

1 think would be also very interested in hearing what has
2 taken place here and what is likely to be thought about
3 for the future is the Joint Commission on Accreditation
4 of Health Organizations.

5 We have talked to them in the past about some
6 of these related issues, and I know they are very
7 interested in being at the table for some of these
8 things.

9 DR. WARD: They are a double-edged sword,
10 though. They can make some very profound efforts and can
11 be very misguided at times.

12 DR. GRAYLOR: You can help them see the right
13 way.

14 DR. WARD: My favorite is just the evaluation
15 of pain in the newborn. It has been, sort of, mandated.
16 Nobody knows how to do it right, but by golly, we are
17 out there doing it, because we have to.

18 Anyhow, there is my platform. I want to thank
19 every one of you for excellent participation and
20 contributions. This has been a very, very thorough
21 process. I think the discussions have been illuminating.
22 I think they have made the outcomes better. I just

1 appreciate everybody taking the time and the effort you
2 have put into it.

3 Thanks so much.

4 [Whereupon, at 3:00 p.m., the proceedings were
5 concluded.]

6 + + +

CERTIFICATION

This is to certify that the attached proceedings

BEFORE THE: NICHD Best Pharmaceuticals
 for Children Act (BPCA)

HELD: October 26, 2004

were convened as herein appears, and that this is the
official transcript thereof for the file of the
Department or Commission.

DEBRA DERR, Court Reporter